HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE

Digitized by the Internet Archive
in 2015

https://archive.org/details/californiamedici1051cali

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
JUL 25 1966

CIRCULATES AFTER AUG 8 1966

California M ine

Serials Department
Health Sciences Library
111 South Greene St.
Baltimore 1, Md.

VOLUME 105 • NUMBER 1

July 1966

~~MAR 8 '67~~, ~~APR 14 '67~~, MAY 27 '67
~~MAR 22 '67~~ ~~MAY 22 1967~~

1 *Phenylketonuria—Early Detection, Diagnosis and Treatment* GEORGE C. CUNNINGHAM, *M.D.*, Berkeley

8 *Cancer of the Larynx—Results of Surgical and Radiological Treatment in One Institution*
L. HENRY GARLAND, *M.B.*, *M.D.*, San Francisco

11 *Rheumatic Fever—Summary of a Rheumatic Fever Workshop on Various Aspects of the Disease*
DONALD C. FYLER, *M.D.*, FORREST H. ADAMS, *M.D.*, CHARLES F. PAIT, *M.D.*, and GEORGE C. GRIFFITH, *M.D.*, Los Angeles

18 *Group Psychotherapy With Adolescents* JOSEPH D. TEICHER, *M.D.*, Los Angeles

22 *Little League Shoulder—Osteochondrosis of the Proximal Humeral Epiphysis in Boy Baseball Pitchers* JOEL E. ADAMS, *M.D.*, San Bernardino

26 *Planing for Precancerous Skin—A Ten-Year Evaluation* ERVIN EPSTEIN, *M.D.*, Oakland

28 *Experience With Dimethyl Sulfoxide* LEONARD MARMOR, *M.D.*, and BARBARA WALIKE, *R.N.*, *M.S.*, Los Angeles

31 *The Chronically Draining Ear—Notes on Management in the Office* JAMES L. SHEEHY, *M.D.*, Los Angeles

35 *The Medical Student* NEWLIN HASTINGS, *M.D.*, Los Angeles

CASE REPORTS

38 *Differentiation of Dysfunction From Rupture of Papillary Muscle*
ROBERT SUDRANN, *M.D.*, and HENRY TESLUK, *M.D.*, Sacramento

41 *Glutethimide Intoxication With Prolonged Coma and Hyperpyrexia Treated With Methylphenidate*
L. A. SCHLEISSNER, *M.D.*, Torrance

MEDICAL STAFF CONFERENCE

45 *Management of Chronic Renal Failure*

CALIFORNIA MEDICAL ASSOCIATION

52 *Council Meeting Minutes, 521st Meeting, 7 May 1966*

INFORMATION

70 *Sources of Income and Principal Employers of California Physicians, August 1965*—Report of the Bureau of Research and Planning.

74 *County Teaching Hospitals*—A Statement of the Council of the California Medical Association

77 EDUCATION NOTICES—MEETINGS AND COURSES

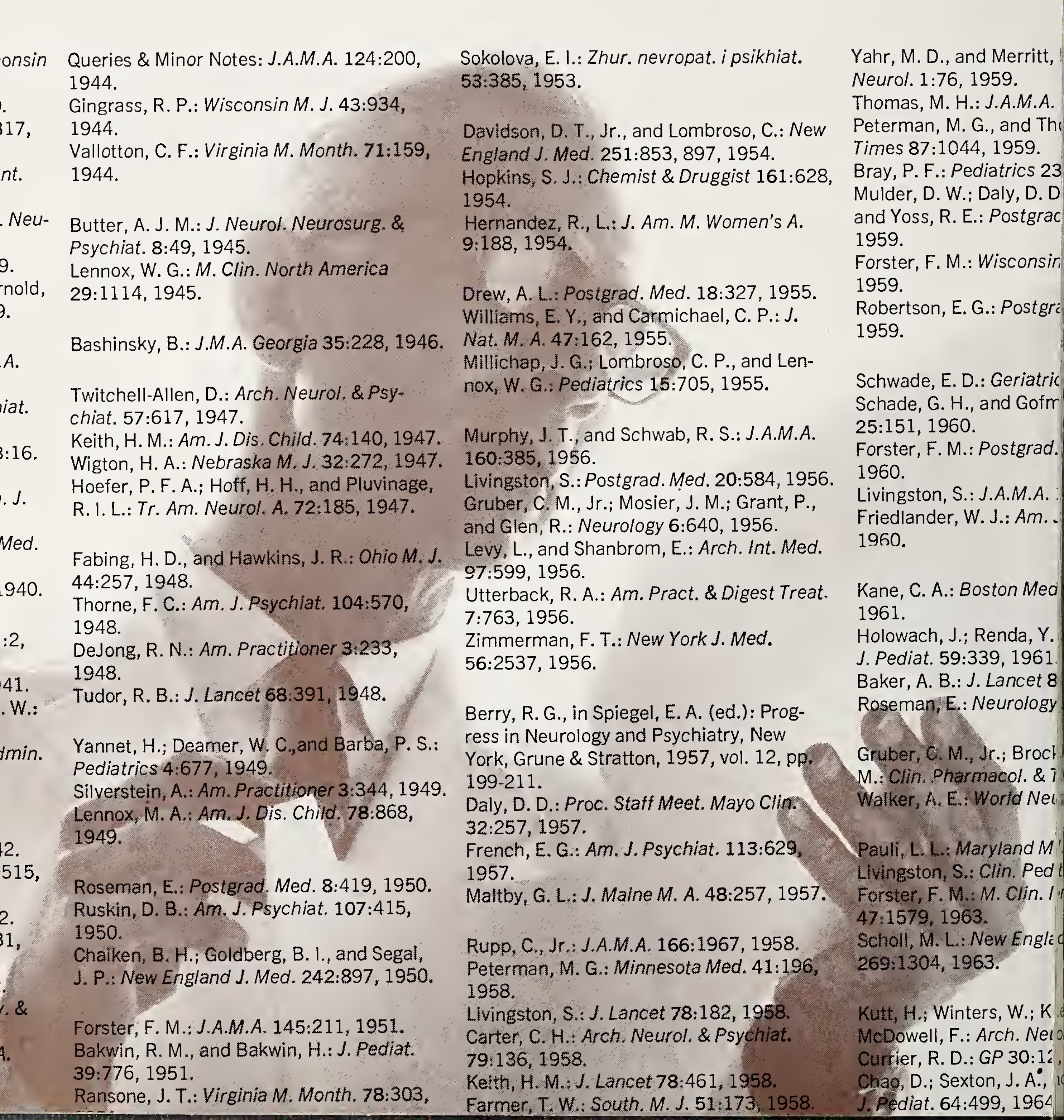
Editorial, 50 *Public Health Report*, 64 *Letters to the Editor*, 66

Woman's Auxiliary, 68 *News and Notes*, 76

1967 ANNUAL MEETING, LOS ANGELES, BILTMORE HOTEL, 15 to 19 APRIL 1967
For Announcement, see page 63

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE



Dilantin®
(diphenylhydantoin)
PARKE-DAVIS

27 years of clinical use... and still the most widely prescribed agent of its kind

Complete information for usage available to physicians on request. 81966

PARKE-DAVIS
PARKE, DAVIS & COMPANY, Detroit, Michigan 48232
1866 1966 100th ANNIVERSARY

Reese, H. H.: *Wisconsin*
.
M. J. 15:344, 1939.
chigan M. Soc. 38:317,

Horan, T. H.: *Ann. Int.*

Putnam, T. J.: *Arch. Neu-*
1053, 1939.
tal Sc. 85:986, 1939.
el, D. L., Jr., and Arnold,
onth. 66:522, 1939.

Osgood, R.: *J.A.M.A.*

ennett, C. L.: *Psychiat.*
0.
: *Washington Bull.* 3:16.

oldstein, H. H.: *Am. J.*
1940.
kson, V.: *Ann. Int. Med.*

d. M.A.J. 43:157, 1940.

Tulane Med. Fac. 1:2,

Times 69:461, 1941.
d Shallenberger, D. W.:
:383, 1941.
d. Bull. Veterans Admin.

cet 61:178, 1941.

Rec. 155:105, 1942.
m. J. Psychiat. 98:515,

M.A. 120:449, 1942.
J. Psychiat. 99:231,

imes 70:244, 1942.
Brenner, C.: *J. Nerv. &*
1942.
Arieff, A. J.: *J.A.M.A.*

Queries & Minor Notes: *J.A.M.A.* 124:200, 1944.
Gingrass, R. P.: *Wisconsin M. J.* 43:934, 1944.
Vallotton, C. F.: *Virginia M. Month.* 71:159, 1944.

Butter, A. J. M.: *J. Neurol. Neurosurg. & Psychiat.* 8:49, 1945.
Lennox, W. G.: *M. Clin. North America* 29:1114, 1945.

Bashinsky, B.: *J.M.A. Georgia* 35:228, 1946.

Twitchell-Allen, D.: *Arch. Neurol. & Psychiat.* 57:617, 1947.
Keith, H. M.: *Am. J. Dis. Child.* 74:140, 1947.
Wigton, H. A.: *Nebraska M. J.* 32:272, 1947.
Hoefer, P. F. A.; Hoff, H. H., and Pluvinage, R. I. L.: *Tr. Am. Neurol. A.* 72:185, 1947.

Fabing, H. D., and Hawkins, J. R.: *Ohio M. J.* 44:257, 1948.
Thorne, F. C.: *Am. J. Psychiat.* 104:570, 1948.
DeJong, R. N.: *Am. Practitioner* 3:233, 1948.
Tudor, R. B.: *J. Lancet* 68:391, 1948.

Yannet, H.; Deamer, W. C.,and Barba, P. S.: *Pediatrics* 4:677, 1949.
Silverstein, A.: *Am. Practitioner* 3:344, 1949.
Lennox, M. A.: *Am. J. Dis. Child.* 78:868, 1949.

Roseman, E.: *Postgrad. Med.* 8:419, 1950.
Ruskin, D. B.: *Am. J. Psychiat.* 107:415, 1950.
Chaiken, B. H.; Goldberg, B. I., and Segal, J. P.: *New England J. Med.* 242:897, 1950.

Forster, F. M.: *J.A.M.A.* 145:211, 1951.
Bakwin, R. M., and Bakwin, H.: *J. Pediat.* 39:776, 1951.
Ransone, J. T.: *Virginia M. Month.* 78:303,

Sokolova, E. I.: *Zhur. nevropat. i psikhiat.* 53:385, 1953.

Davidson, D. T., Jr., and Lombroso, C.: *New England J. Med.* 251:853, 897, 1954.
Hopkins, S. J.: *Chemist & Druggist* 161:628, 1954.
Hernandez, R., L.: *J. Am. M. Women's A.* 9:188, 1954.

Drew, A. L.: *Postgrad. Med.* 18:327, 1955.
Williams, E. Y., and Carmichael, C. P.: *J. Nat. M. A.* 47:162, 1955.
Millichap, J. G.; Lombroso, C. P., and Lennox, W. G.: *Pediatrics* 15:705, 1955.

Murphy, J. T., and Schwab, R. S.: *J.A.M.A.* 160:385, 1956.
Livingston, S.: *Postgrad. Med.* 20:584, 1956.
Gruber, C. M., Jr.; Mosier, J. M.; Grant, P., and Glen, R.: *Neurology* 6:640, 1956.
Levy, L., and Shanbrom, E.: *Arch. Int. Med.* 97:599, 1956.
Utterback, R. A.: *Am. Pract. & Digest Treat.* 7:763, 1956.
Zimmerman, F. T.: *New York J. Med.* 56:2537, 1956.

Berry, R. G., in Spiegel, E. A. (ed.): Progress in Neurology and Psychiatry, New York, Grune & Stratton, 1957, vol. 12, pp. 199-211.
Daly, D. D.: *Proc. Staff Meet. Mayo Clin.* 32:257, 1957.
French, E. G.: *Am. J. Psychiat.* 113:629, 1957.
Maltby, G. L.: *J. Maine M. A.* 48:257, 1957.

Rupp, C., Jr.: *J.A.M.A.* 166:1967, 1958.
Peterman, M. G.: *Minnesota Med.* 41:196, 1958.
Livingston, S.: *J. Lancet* 78:182, 1958.
Carter, C. H.: *Arch. Neurol. & Psychiat.* 79:136, 1958.
Keith, H. M.: *J. Lancet* 78:461, 1958.
Farmer, T. W.: *South. M. J.* 51:173, 1958.

Yahr, M. D., and Merritt,
Neurol. 1:76, 1959.
Thomas, M. H.: *J.A.M.A.*
Peterman, M. G., and Th
Times 87:1044, 1959.
Bray, P. F.: *Pediatrics* 23
Mulder, D. W.; Daly, D. D
and Yoss, R. E.: *Postgrac*
1959.
Forster, F. M.: *Wisconsin*
1959.
Robertson, E. G.: *Postgr*
1959.

Schwade, E. D.: *Geriatric*
Schade, G. H., and Gofm
25:151, 1960.
Forster, F. M.: *Postgrad.*
1960.
Livingston, S.: *J.A.M.A.*
Friedlander, W. J.: *Am.*
1960.

Kane, C. A.: *Boston Med*
1961.
Holowach, J.; Renda, Y.
J. Pediat. 59:339, 1961.
Baker, A. B.: *J. Lancet* 8
Roseman, E.: *Neurology*

Gruber, C. M., Jr.; Broc
M.: *Clin. Pharmacol. &*
Walker, A. E.: *World Ne*

Pauli, L. L.: *Maryland M*
Livingston, S.: *Clin. Ped*
Forster, F. M.: *M. Clin.*
47:1579, 1963.
Scholl, M. L.: *New Engla*
269:1304, 1963.

Kutt, H.; Winters, W.; K
McDowell, F.: *Arch. Ne*
Currier, R. D.: *GP* 30:1
Chao, D.; Sexton, J. A.,
J. Pediat. 64:499, 1964

Terrastatin®

Capsules
oxytetracycline 250 mg., nystatin 250,000 units
For Oral Suspension
oxytetracycline 125 mg., nystatin 125,000 units/5 cc.

Contraindicated: In individuals hypersensitive to oxytetracycline or nystatin.

Warning: Reduce usual oral dosage and consider antibiotic serum level determinations in patients with impaired renal function.

Use of oxytetracycline during the last trimester of pregnancy, neonatal period and early childhood may cause discoloration of developing teeth.

During treatment with tetracyclines, individuals susceptible to photodynamic reactions should avoid direct sunlight; if such reactions occur, discontinue therapy.

Note: With oxytetracycline, phototoxicity is unknown and photoallergy very rare.

Precautions: Use of broad-spectrum antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Where such infections occur, discontinue oxytetracycline and institute specific therapy. Increased intracranial pressure in infants is a possibility. Symptoms disappear upon discontinuation of therapy.

Adverse Reactions: Nausea, diarrhea, glossitis, stomatitis, proctitis, vaginitis and dermatitis, as well as reactions of an allergic nature, may occur but are rare.

Supply: Terrastatin Capsules: oxytetracycline, 250 mg. and nystatin, 250,000 units. Terrastatin for Oral Suspension: oxytetracycline, 125 mg. and nystatin, 125,000 units per 5 cc. (when reconstituted).

More detailed professional information available on request.

Science for the world's well-being®

Pfizer

Since 1849

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
New York, New York 10017

Annual Report on Medical Licensure

Another 8,943 licensed physicians were added to the U.S. medical profession in 1965, according to a report by the American Medical Association's Council on Medical Education.

The total is 1,032 more than the number of physicians newly licensed in 1964.

As of December 31, 1965, there were 292,088 physicians in the U.S. This number includes 239,623 licensed physicians, a net gain of 5,286—after deaths, retirements, etc.—from the same date a year earlier. (The 52,465 unlicensed physicians, most of whom contribute to patient care, include many interns and residents, military and government-service doctors, some medical educators, administrators, and retired physicians.)

The AMA's 64th annual report on medical licensure statistics appears in the June 6 *Journal of the AMA*.

Of all newly licensed physicians, 7,445 attended U.S. and Canadian medical schools; the remaining 1,488 were graduates of foreign medical faculties. In recent years, about one-quarter of foreign-trained graduates issued first licenses have been Americans who attended medical schools outside the U.S. and Canada.

Of ten geographical regions of the U.S., all but one showed increases in newly licensed physicians of from 6 to 39 per cent during 1965. The seven-state region of Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, and Utah had a 24 per cent decline.

New York had the greatest number of physicians receiving their first licenses—1,192. This was 233 more than in 1964. California was again second with 1,045 new licentiates; 228 more than the previous year. Pennsylvania had 582; Texas, 497; Ohio, 456.

Eight other states each had more than 200 newly licensed physicians in 1965—Illinois, Michigan, Maryland, Virginia, Georgia, Louisiana, Missouri, and North Carolina.

Kentucky showed the most notable increase in new licenses awarded—147 in 1965, compared with 33 in 1964.

A total of 17,812 licenses to practice medicine and surgery were issued during 1965 by 54 authorized boards in the U.S. and its territories. In addition to first licenses, these included licenses for physicians moving from one state to another.

For the third successive year, California led all states in the total number of licenses issued with 2,657—34 more than the previous year. New York was second with 2,232; Pennsylvania was third with 938; Ohio, fourth with 907. Texas, Illinois, Maryland, Michigan, Virginia, and Florida followed in that order; each issued somewhat more than 500 licenses.

The fewest licenses were issued by Montana

(Continued on Page 22)

because relief means so much to your G.U. patient

There are not many drug combinations in use today which can claim to have served the medical profession for more than 50 years. Such a record reflects the continued confidence of physicians in URISED. This is not a dramatic "wonder drug" — but a *useful* one.

URISED is safe . . . especially useful in long-term management of chronic cases; as a prophylactic measure with catheterization or after instrumentation. No systemic reactions or bacterial resistance have been reported.

URISED rapidly exerts spasmolytic action, relieving pain and discomfort of urgency, frequency, and burning on urination. Rapid acting URISED exerts antibacterial action against uropathogens susceptible to methenamine and methylene blue, in an acid medium.

URISED®

Each blue-coated tablet contains active:

Atropine Sulfate	0.03 mg.	Methylene Blue	5.4 mg.
Hyoscyamine	0.03 mg.	Phenyl Salicylate	18.1 mg.
Methenamine	40.8 mg.	Gelsemium	6.1 mg.
		Benzoic Acid	4.5 mg.

PRECAUTIONS: Administer with caution to persons with glaucoma or atropine idiosyncrasy.

SIDE EFFECTS: If rapid pulse, dizziness or blurring of vision occurs, discontinue use. If dryness of mouth occurs, decrease dosage. Acute urinary retention may be precipitated in prostatic hypertrophy.

CONTRAINDICATIONS: Myasthenia gravis.

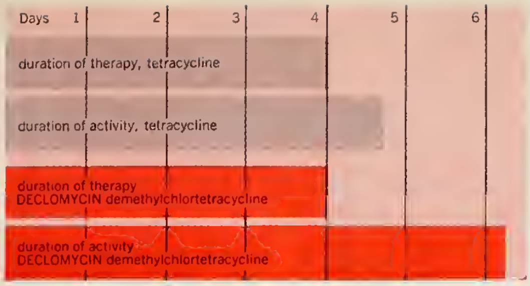
DOSAGE: Adults—Two tablets, orally, four times per day followed by liberal fluid intake. Acute cases—Initially two tablets every hour for three doses followed by the recommended daily administration. Children—One-half the adult dose.

Stocked Nationally Through All Service Wholesale Druggists

CONAL
PHARMACEUTICALS, INC.
CHICAGO, ILLINOIS 60640

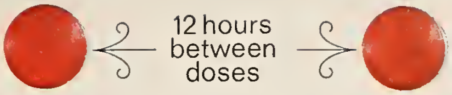
MANUFACTURERS OF URICEUTICAL® SPECIALTIES

• CYSTOSPAZ® • URISEDAMINE® • ŪTRASUL® Tablets and Suspension



1-2 days' "extra" activity

after the last dose to protect against relapse



one 300 mg Tablet mid-morning

one 300 mg Tablet mid-evening

It's made for b.i.d.

in G.U. infections

broad-spectrum performance above and beyond the activity of ordinary tetracyclines

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE

Effective in a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill—when the offending organisms are tetracycline-sensitive.

Contraindication—History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive systemic accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of discomfort.

Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York Lederle
656-6-3762

★

Specialized Service
IN
PROFESSIONAL LIABILITY
INSURANCE

is a high mark
of distinction

THE
MEDICAL PROTECTIVE COMPANY
FORT WAYNE, INDIANA
Professional Protection Exclusively since 1899

NORTHERN CALIFORNIA OFFICE:
Gordon C. Jones and John K. Galloway, Representatives
1518 Fifth Avenue, San Rafael, Telephone: 415-453-5140
Mailing Address: P.O. Box 1079, San Rafael 94902
SOUTHERN CALIFORNIA OFFICE:
Davis S. Spencer and Grady T. Dyer, Representatives
Suite 3, 33 East Huntington Drive, Arcadia, Tel. 213-681-5239
Mailing Address: P.O. Box 543, Arcadia 91008

PARAMUS COIN EXCHANGE
The East's Largest Coin Exchange
OFFERS U.S. GOLD FOR YOUR FUTURE
ALL BRILLIANT UNCIRCULATED

$20 Gold pieces
Liberty $ 54.95
St. Gaudens $ 54.95
$10 Gold pieces
Liberty $ 32.95
Indian $ 52.95
$5 Gold pieces
Liberty $ 24.95
Indian $ 32.95
$3 Gold pieces
$349.00
$2.50 Gold pieces
Liberty $ 52.95
Indian $ 32.95
$1 Gold pieces
Type 1 $ 49.95
Type 2 $250.00
Type 3 $ 75.00

SETS
Liberty Gold Type Set 4 Coins $159.95
Indian Gold Type Set 4 Coins $169.95
All Coins in Custom Plastic Cases

U. S. SILVER DOLLARS BRILLIANT UNCIRCULATED
Single $2.00
Roll $39.95
Bag $1695.00
Gold and Silver Is Today's Best Investment

Paramus Coin Exchange
Bergen Mall Shopping Center
Paramus, N.J. 07652
A.N.A. Member
201-342-2600
Gentlemen: Please ship the following:

Name
Address
City State
Bill My D.C. Acct. #
Bill My Amer. Exp. Acct. #
For other coin values send for free catalogue!

Average U.S. Health Expense Ranges From $61 to $208

The average American had an annual health expense of $129 during 1962, data collected in the Department of HEW's Health Interview Survey shows, according to the National Association of Blue Shield Plans.

This expense increased directly with age, ranging from $61 for children under six, to $208 for persons 65 and over.

Included as health expenditures were physician expense, hospital in-patient expense, medicine costs, dentist expense, and special or other medical expense such as eye glasses, speech therapy, wheel chairs, and emergency or out-patient treatment in a hospital or clinic.

Physician expense represented about one-third of the total health expenses in the population, and regardless of sex and age, was invariably greater than any of the other four categories of health expense. Total health expense increased with the educational level of the family head and with the level of family income.

Annual Report on Medical Licensure

(Continued from Page 13)

(19). Alaska, Delaware, Idaho, New Mexico, Nevada, North and South Dakota, and Wyoming each issued fewer than 50 licenses in 1965.

There also were 1,250 unlimited licenses to practice medicine issued to osteopathic physicians in 1965.

"The fact that there were more osteopathic licenses issued by (state) endorsement than by examination suggests that there may have been more osteopathic physicians migrating (from one state to another) in 1965 than there were new additions to the practicing profession," the *Journal* report said.

A second section of the Council's report pertains to examinations and endorsement of credentials sponsored by 24 boards of examiners in the basic sciences in 23 states and the District of Columbia.

A third section deals with examinations given by the National Board of Medical Examiners.

The fourth section summarizes results of the examination given to foreign-trained physicians by the Educational Council for Foreign Medical Graduates.

The report was compiled by the AMA staff under the supervision of Walter S. Wiggins, M.D., secretary of the Council; A. N. Taylor, Ph.D., associate secretary; and Henry R. Mason, M.P.H., assistant secretary.

W. Clarke Wescoe, M.D., chancellor of the University of Kansas, is chairman of the Council on Medical Education. Kenneth C. Sawyer, M.D., Denver, Colorado, is vice-chairman.

before he started on Obedrin-LA

- Gives 1-a-day freedom from overactive appetite—"trickle release" for smooth, sustained all-day action
- Suppresses appetite and lifts mood
- Allays anxiety and counteracts excess stimulation
- Nutritional supplement for patients on restricted diets

Dosage: 1 tablet daily, usually at 10 a.m.

Supplied: Bottles of 50 and 250 on prescription only.

Caution: Obedrin-LA should not be given concurrently with monoamine oxidase inhibitors. It should be used with caution in patients having a sensitivity to sympathomimetic compounds or barbiturates and in cases of coronary or cardiovascular disease or severe hypertension. Excessive use of amphetamines by unstable individuals has been reported to result in a psychological dependence. In such instances, withdrawal of the medication is necessary. All medication should be used with caution in pregnant patients, especially in the first trimester.

†of Chestnut Hill, Pa.

Obedrin®-LA*

"TRICKLE RELEASE" TABLETS

Each tablet contains: Methamphetamine HCl*, 12.5 mg.; Pentobarbital*, 50 mg. (Barbituric Acid derivative; Warning: May be habit forming), Ascorbic Acid, 200 mg.; Thiamine Mononitrate, 1 mg.; Riboflavin, 2 mg.; Niacin, 10 mg. *U.S. Pat. Nos. 2,736,682; 2,809,916; 2,809,917; 2,809,918 and pat. pend.

MASSENGILL The S. E. Massengill Company, Bristol, Tennessee

New York • San Francisco • Dallas • Chicago • Kansas City

THE BLUE CHIP
STOCK
*In Generic
Pharmaceuticals*

Towne
ASSURANCE
OF OPTIMUM
CLINICAL
EFFECTIVENESS

Pharmacies everywhere now stock TOWNE generic pharmaceuticals. Prescribe TOWNE to assure your patients of consistent high quality and uniformity ...at sensible prices.

PARTIAL LIST OF PRODUCTS

DIOCTYL SODIUM SULFOSUCCINATE N.F.
(S.G. capsules: 100mg—250mg)
HEPARIN INJECTION
(10M—20M—40M USP Units/cc)
C. T. MEPROBAMATE N.F.
(200mg—400mg)
C. T. PENICILLIN G USP
(200M—250M—400M Units)
C. T. PREDNISONE USP
(2.5mg—5mg)
C. T. QUINIDINE USP
(3 gr.)
C. T. RESERPINE USP
(0.1mg—0.25mg—1mg)
TETRACYCLINE HCL USP
(H.S. capsules—250mg—Domestic material)

Product List available on request.

Towne PRESCRIPTION PRODUCTS DIVISION

Towne, Paulsen & Company, Inc.
Pharmaceutical Chemists Monrovia, California

Favorite Targets of Mosquitoes

Mosquitoes play favorites among those they bite.

According to the July *Today's Health* magazine, published by the American Medical Association, certain characteristics may make you a stand-out target for mosquitoes.

You're most likely to be bitten if you:

—*Have a dark complexion.* In experiments at the University of Western Ontario, naturally dark-skinned persons attracted 22 per cent more mosquitoes than light-skinned persons. Orientals attracted 27 per cent more mosquitoes than Caucasians, and Negroes attracted 60 per cent more than white persons.

—*Are warm-skinned.* The average internal temperature of healthy humans doesn't vary much from 98.6°F, but there is a considerable variation in skin temperatures. Experiments showed that warm-skinned persons attracted 30 per cent more mosquitoes than those with cooler skins.

—*Are in good health.* Researchers at Union Carbide Corporation discovered that mosquitoes put the bite on healthy "outdoorsy" types much more frequently than on persons in poor health.

—*Perspire moderately.* The more a person perspires—up to a point—the higher his "attractivity index" to mosquitoes.

—*Breathe heavily.* Apparently it is the carbon dioxide in expired air that helps guide the mosquito to its target.

—*Are highly active.* The energetic person constantly on the move is the one that attracts the mosquito's attention.

—*Wear perfume, cologne, or after-shave lotion.* Anything with a "noticeable fragrance" seems to bring on the bites.

—*Wear dark clothing.* Cloth of 32 textures and colors has been studied, and without exception the less light that a material reflected, the more attractive it was to mosquitoes. Stated another way, the duller your clothing, the more attractive you'll be to mosquitoes. They prefer black, dark reds and dark blues instead of white, yellows, and light greens.

The author, Clifford B. Hicks, points out that you can minimize mosquito attacks this summer. Dress in light clothing, bathe frequently, cut down on strenuous activity, and take it easy on perfumes and after-shave lotions.

There are more than 2,500 species of mosquito, but one type, Culex pipiens, is the most common in the United States. It's the female, incidentally, which bites humans.

Most household mosquitoes travel no more than two or three city blocks during their lives, a fact which is important to community mosquito con-

(Continued on Page 29)

Favorite Targets of Mosquitoes

(Continued from Page 26)

trol. If your community should eliminate all breeding spots, such as pools of stagnant water, old auto tires, open cans, etc., the problem of mosquito bites would be greatly reduced, and perhaps gone forever.

An Editorial on Automobile Accidents

An editorial in the May 30 *Journal of the American Medical Association* has this to say about automobile accidents:

"Directing attention to the 'nut behind the wheel' is worthwhile as long as we do not permit two fallacies to direct research policy. The first fallacy is that identifying all 'nuts' (however one defines the term) is possible.

"The second fallacy is that, even if possible, this identification could be used so as to prevent all or most traffic accidents.

"Collisions frequently are caused by momentary inattention, by sudden unpredictable changes in climate or road conditions, by faulty tires producing blowouts, and by poor automobile design or construction. These factors can involve the most careful and skillful driver in an accident.

"In a way, our attitude toward automobile safety in the past seems punitive. By ignoring research into more crashworthy vehicles, we seem to have been implying: if you are stupid enough, or criminal enough to be involved in an accident, you deserve the consequences."

More research is needed on the "second collision" in an auto crash, the editorial said. This second collision occurs when occupants strike the vehicle's interior after the car collides with another object.

"Despite general lack of interest in second-collision research a few individuals have worked on this problem," the editorial said. "They have shown that many dangerous features in our cars can be corrected at once, without further research.

"The interior of our cars must be stripped of sharp handles and protruding knobs. Adequate padding must be provided throughout the automobile. The chest-crushing potentiality of the steering column must be eliminated."

The number of persons who don't use their seat belts indicates how difficult it is to motivate drivers to protect themselves, the editorial said.

"Yet the belts seem unquestionably helpful in preventing significant numbers of fatalities, and there is further evidence that a combination seat-belt-shoulder-harness offers even more protection."

One of the many things physicians can do to help reduce highway deaths is to advise their patients, the editorial said. "They deserve to know what risks they take when they drive, and they deserve to know how necessary—or unnecessary—these risks are."

Little-known moments in history No. 1:

Mr. Ra, a sculptor, was commissioned by Queen Nefertiti to do a statue of herself, and by King Tut to do a large lion for his front lawn. Confused by vertigo, Mr. Ra got the whole thing mixed up. Did he get a royal bawling-out!

Antivert® stops vertigo tablets · syrup

(meclizine HCl, nicotinic acid)

Tablets: (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.)
Syrup: (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.)

Most widely prescribed anti-vertigo agent[1]
Complete to moderate relief in 9 out of 10 patients[2]

Antivert, the leading anti-vertigo product,[1] combines meclizine HCl, an outstanding drug for treatment of vestibular dysfunction, with nicotinic acid, a drug of choice for prompt vasodilation. Prescribe Antivert for your patients with vertigo, Meniere's syndrome or allied disorders.

Precautions and contraindications: Frequent, short-lived reactions include: cutaneous flushing, sensations of warmth, tingling and itching, burning of skin, increased gastrointestinal motility, and sebaceous gland activity. In explaining these reactions to the patient, it is suggested that they be regarded as a desirable physiological sign that the nicotinic acid is carrying out its intended function of vasodilation. Because of this vasodilation, severe hypotension and hemorrhage are obvious contraindications to Antivert therapy. Although the incidence of drowsiness and other atropine-like side effects such as dry mouth and blurring of vision is low, the physician should alert the patient to the need for due precautions when engaging in activities where alertness is mandatory. **Use in pregnancy:** A review of available animal data reveals that meclizine exerts a teratogenic response in the rat. While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human fetus. Consequently, consideration should be given to initial use of a nonphenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum.

Dosage: One tablet or one to two teaspoonfuls (5-10 cc.) t.i.d. just before meals. Specific requirements for individual patients should be determined by the physician.

Supplied: Tablets in bottles of 100 and 500. Syrup in pint bottles. Rx only.

References: 1. Based on 1965 data from independent physicians' market survey organization. 2. Scal, J. C.: Eye Ear Nose & Throat Month. 38:738 (Sept.) 1959.

J. B. Roerig and Company
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®
New York, N. Y. 10017

DIRECTORY

HOSPITALS • SANITARIUMS • REST HOMES

Exclusively for the treatment of
ACUTE AND CHRONIC
ALCOHOLISM

Woodside Acres Hospital
MEMBER AMERICAN HOSPITAL ASSOCIATION
1600 Gordon Street Redwood City, California
EMerson 8-4134

COMPTON FOUNDATION HOSPITAL
FORMERLY COMPTON SANITARIUM
820 West Compton Boulevard
COMPTON, CALIFORNIA
NE 6-1185 NE 1-1148

G. CRESWELL BURNS, M.D.
Medical Director
HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association and
National Association of Private Psychiatric Hospitals
High Standards of Psychiatric Treatment
. . . . . . Serving the Los Angeles Area

Fully Approved by Central Inspection Board of APA

Accredited by
Joint Commission on Accreditation of Hospitals

Belmont hills foundation, inc.
ADOLESCENT TREATMENT CENTER
The adolescent treatment center offers intensive treatment to disturbed youngsters of both sexes ranging from age 12 through 18. A "therapeutic community" program is offered for both Residential (24 hour) and Partial (day or night) care youngsters. In addition to a comprehensive diagnostic evaluation on admission, the following treatment modalities are utilized: Individual and group psychotherapy, occupational and recreational therapy. Schooling is provided by individual tutoring.

Address inquiries:
HARVEY J. NEWTON, M.A., M.D.
RONALD J. SOVAK, M.S.W., *Clinical Director*
P. O. Box 37
Belmont, California
(415) 593-2143

Barlow Sanatorium For Tuberculosis
Partially endowed private eleemosynary hospital for Pulmonary Tuberculosis patients with hopeful prognosis, or diagnostic problems of diseases of the chest • Sliding scale of rates from $8.00 to $25.00 per day according to ability to pay. Includes medical supervision, routine nursing care, laboratory services, x-ray and ordinary drugs. • Accredited by Joint Commission on Accreditation of Hospitals • Affiliated with University of Southern California Medical School • Member of Western Hospital Association, California Hospital Association and Hospital Council of Southern California • Apply by contacting Medical Director or Assistant Medical Director, or by direct referral through morning clinic.

2000 STADIUM WAY, CHAVEZ RAVINE, LOS ANGELES,
CALIFORNIA 90026 MAdison 8-4165

HOWARD W. BOSWORTH, M.D., *Medical Director*
FRANKLIN S. REDING, M.D., *Assistant Medical Director*

Twin Pines
NEUROPSYCHIATRIC HOSPITAL
OPEN, VISITING AND CONSULTING STAFF
BELMONT, CALIFORNIA ESTABLISHED 1925

In-patient services for acute and chronic emotional illnesses.
Electric shock Insulin shock
Hydrotherapy Psychotherapy
Occupational therapy

Out-patient services for selective cases

Attending Staff
A. T. VORIS, M.D., Medical Director
DAVID S. WILDER, M.D. • ROBERT E. JAMES, M.D.
ALEXANDER H. MILNE, M.D. • ROBERT L. MEIERS, M.D.

LYtell 1-8951
Located 22 miles south of San Francisco. Accessible to transportation.

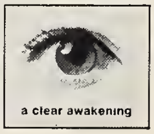
a good night's sleep with

Doriden® (glutethimide CIBA)

Doriden is particularly suitable for hypertensive patients with insomnia for, unlike barbiturates, it has virtually no effect on pulmonary or kidney function. It rarely, if ever, causes respiratory depression. Doriden is well tolerated by the chronically ill—may even be prescribed for hypertensives with renal involvement.

The "healthy" patient with insomnia, as well as those who are sick, will benefit from the ability of Doriden to induce sound sleep quickly with virtually no pre-excitation. With Doriden, patients can expect a good night's sleep and awake refreshed—usually free from barbiturate-like "hangover."

INDICATIONS AND DOSAGE: *Insomnia*—0.5 Gm at bedtime. *Preoperative Sedation*—0.5 Gm the night before surgery; 0.5 to 1 Gm 1 hour before anesthesia. *Obstetric Sedation*—0.5 Gm at onset of labor. Continuing total daily dosage over 1 Gm is not recommended. CAUTION: Supervise dosage carefully, especially in patients with a known propensity for overdosing. Excessive and prolonged use in susceptible persons (*e.g.*, alcoholics, former addicts, severe psychoneurotics) may result in dependence and withdrawal reactions such as nausea, abdominal discomfort, tremors, or convulsions. Newborns of mothers dependent on glutethimide may exhibit withdrawal symptoms. SIDE EFFECTS: Occasionally, a skin rash may occur; if so, withdraw drug. The rash usually clears spontaneously in 2 or 3 days. Occasionally nausea also occurs. Rarely, acute hypersensitivity reactions and blood dyscrasias have been associated with glutethimide therapy. SUPPLIED: *Tablets*, 0.5 Gm (white, scored) and 0.25 Gm (white, scored); bottles of 100, 500 and 1000. *Tablets*, 0.125 Gm (white); bottles of 100. *Capsules*, 0.5 Gm (blue and white); bottles of 100
Consult complete literature before prescribing
CIBA Pharmaceutical Company, Summit, N. J.



CIBA Summit, N. J. 2/3436 MBM

Economical Long-term Therapy for Iron Deficiency Anemia

Tablets & Elixir

FAMOUS Fergon®
brand of FERROUS GLUCONATE

C.M.A.P. CODE # 5261

BREON LABORATORIES INC.
Subsidiary of Sterling Drug Inc.
90 Park Avenue, New York, N.Y. 10016

LSD Warning Still Applies

Most of those who have suffered ill effects from taking the drug, LSD (lysergic acid diethylamide), probably didn't listen to the advice of physicians.

As early as September 1963, an editorial in the *Journal of the American Medical Association* warned of possible dangers in the hallucination-producing agents, including LSD.

The advice still applies, says the author, Dana L. Farnsworth, M.D., director of health services and the H.K. Oliver Professor of hygiene at Harvard University.

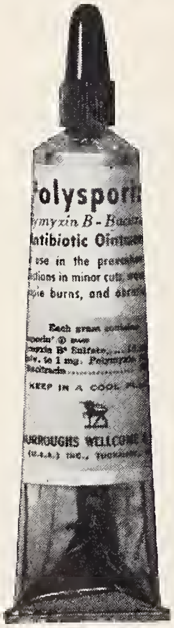
"Recent clinical observations . . . suggest that people who are attracted to the hallucinogenic drugs are often those most likely to be harmed by them," said Dr. Farnsworth's 1963 editorial.

"Many who have tried the drugs were persons who had difficulty dealing with reality, who sought in drugs a quick and easy method of changing reality, and who hoped for a prompt solution to their inner conflicts."

Experience with patients demonstrated "beyond question," Dr. Farnsworth said, that the hallucinogenic drugs "have the power to damage the individual psyche, perhaps to cripple it for life."

There is no easy way to identify those for whom the drug is "safe," he said. Neither can it be

(Continued on Page 42)



in treating topical infections, no need to sensitize the patient

USE 'POLYSPORIN'® brand
POLYMYXIN B-BACITRACIN
ANTIBIOTIC OINTMENT

broad-spectrum antibiotic therapy with minimum risk of sensitization

Caution: As with other antibiotic products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **Contraindication:** This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.
Supplied: In ½ oz. and 1 oz. tubes
Complete literature available on request from Professional Services Dept. PML.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF MEDICINE, Vol. 17, 1966—Arthur C. De Graff, Editor, New York University College of Medicine; and William P. Creger, Associate Editor, Stanford University School of Medicine. Annual Reviews, Inc., Palo Alto, Calif., 1966. 563 pages. The price, postpaid, for the current and all back volumes of the Annual Review of Medicine is $8.50 per copy (U.S.A.) and $9.00 (elsewhere). (California residents subject to 4 per cent sales tax.) Student rate information available.

BLOOD DISEASES OF INFANCY AND CHILDHOOD—Second Edition—Carl H. Smith, M.A., M.D., Clinical Professor of Pediatrics, Cornell University Medical College, New York, N.Y.; Consulting Pediatrician, The New York Hospital, New York, N.Y.; Beckman-Downtown Hospital, New York, N.Y. The C. V. Mosby Company, St. Louis, Mo., 1966. 800 pages, $22.00.

CELL WATER—D. A. T. Dick, M.B., Ch.B. (Glas.), M.A., D.Phil. (Oxon), University Lecturer in Anatomy, University of Oxford; Fellow of St. Cross College, Oxford, England. Butterworths, Washington, D.C., 1966. 155 pages, $6.95.

CURRENT PSYCHIATRIC THERAPIES, Vol. VI—1966—An Annual Publication—Edited by Jules H. Masserman, M.D., Professor and Co-Chairman of Psychiatry, Northwestern University, Chicago, Illinois. Grune & Stratton, Inc., New York, N.Y., 1966. 382 pages, $13.50.

HERITABLE DISORDERS OF CONNECTIVE TISSUE—Third Edition—Victor A. McKusick, M.D., Professor of Medicine, The Johns Hopkins University School of Medicine; Physician, The Johns Hopkins Hospital, Baltimore. The C. V. Mosby Company, St. Louis, Mo., 1966. 499 pages, $18.50.

MEDICAL DEPARTMENT, UNITED STATES ARMY IN WORLD WAR II (The Technical Services)—Medical Service in the Mediterranean and Minor Theaters, by Charles M. Wiltse, chief historian; Office of the Chief of Military History, Department of the Army, Washington, D.C., 1965. 664 pages; for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, $5.00.

NEW DRUGS—Evaluated by the A.M.A. Council on Drugs—1966. Published by the American Medical Association, Chicago, Illinois. 591 pages. Prices: U.S., U.S. Possessions, Canada, Mexico, $4.00 per copy; all other countries, $5.00 per copy; Medical students, Interns, Residents, $3.00 per copy (U.S., U.S. Possessions, Canada and Mexico).

PATHOLOGY ANNUAL: 1966, Volume I—Series Editor, Sheldon C. Sommers, M.D., Professor of Pathology, Columbia University College of Physicians and Surgeons; Associate Director of Laboratories, Francis Delafield Hospital, New York, New York; Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif. Appleton-Century-Crofts (Division of Meredith Publishing Company) New York, 1966. 387 pages, $12.00.

SCIENCE AND PSYCHOANALYSIS — Volume IX — Adolescence, Dreams and Training—Edited by Jules H. Masserman, M.D., Professor and Co-Chairman of Psychiatry, Northwestern University, Chicago. Grune & Stratton, Inc., New York, 1966. 205 pages, $7.75.

SURGICAL APPROACHES TO THE NECK, CERVICAL SPINE AND UPPER EXTREMITY—Emanuel B. Kaplan, M.D., formerly Associate Professor of Clinical Anatomy, College of Physicians and Surgeons, Columbia University, New York City; Consultant in Orthopedic Surgery, Director of Hand Surgery, Hospital for Joint Diseases, New York City; Consultant in Orthopedic Surgery, Bronx Lebanon Center, New York City, and St. Joseph's Hospital, Paterson, New Jersey. W. B. Saunders Company, Philadelphia, Pa., 1966. 246 pages, $11.50.

SYMPOSIUM ON VASCULAR DISORDERS OF THE EYE—Basic considerations in anatomy and physiology—Sponsored by The Visual Sciences Study Section, Division of Research Grants, N.I.H. (P.H.S. Conference Grant NB 05516-01 from the National Institute of Neurological Diseases and Blindness) and The Department of Ophthalmology, Presbyterian Medical Center, San Francisco. Subcommittee on vascular disorders: Jerome W. Bettman, Chairman; Raymond A. Allen; Calvin Hanna and Marie A. Jakus. Advisers to the committee: Edward W. D. Norton and Kenneth Swan. From articles appearing in the December 1965 issue of Investigative Ophthalmology. The C. V. Mosby Company, St. Louis, Mo., 1966. 186 pages, $12.50.

Your public relations problem has been our prime consideration in collection procedures during two generations of ethical service to the Medical Profession.

THE DOCTORS BUSINESS BUREAU
Since 1916
821 MARKET ST., SAN FRANCISCO 94103
GArfield 1-0460

For topical treatment of DENUDED and PAINFUL SKIN LESIONS

Anti-Pyrexol antiseptic ointment reduces pain, minimizes scarring, aids healing of burns, sunburn, scalds, lesions, wounds, and local inflammation of skin and mucous membrane. Sold through surgical supply houses. 1, 5, 10 and 50 lb. tins. Time tested—professionally since 1921. Active ingredients: Oils of spearmint, bay, wintergreen (syn.), salicylic acid, lanolin, zinc oxide, phenol .44%, ortho-hydroxyphenyl-mercuric chloride .056%, petrolatum, paraffin.

Anti-Pyrexol Benzocaine. Acutely anesthetic. Contains Benzocaine 3%. 1, 5 and 10 lb. tins.

EASY SPREADING
Anti-Pyrexol
KIP, INC.—LOS ANGELES 21

STACEY'S for any Medical Book in Print
Retail Stores in Palo Alto and San Francisco

NEW BOOK

HUMAN SEXUAL RESPONSE. By William H. Masters, M.D., and Virginia E. Johnson. 366 pages. Illustrated. 1966. Little, Brown. $10. Kinsey opened the doors of contemporary culture to the study of human sexuality. But Masters and Johnson have taken sexology one step further by actually measuring the physiologic and psychologic responses of men and women to sexual stimulation. The product of eleven years' research, this pioneering effort is a unique contribution to medical knowledge.

Stacey's
326-9955
2575 HANOVER STREET
PALO ALTO, CALIFORNIA 94304

Please send me on approval: ____________

Name ____________
Street ____________
City ____________ State ____________

good reason
to select
Ilosone®
Erythromycin Estolate
for bacterial
infections

two to four times
the therapeutic
activity of other
erythromycins

CONTRAINDICATIONS: Ilosone is contraindicated in patients with a known history of sensitivity to this drug and in those with preexisting liver disease or dysfunction.

SIDE-EFFECTS: Even though Ilosone is the most active oral form of erythromycin, the incidence of side-effects is low. Infrequent cases of drug idiosyncrasy, manifested by a form of intrahepatic cholestatic jaundice, have been reported. There have been no known fatal or definite residual effects. Gastro-intestinal disturbances not associated with hepatic effects are observed in a small proportion of patients as a result of a local stimulating action of Ilosone on the alimentary tract. Although allergic manifestations are uncommon with the use of erythromycin, there have been occasional reports of urticaria, skin eruptions, and, on rare occasions, anaphylaxis.

DOSAGE: *Children under 25 pounds*—5 mg. per pound of body weight every six hours. *Children 25 to 50 pounds*—125 mg. every six hours. *Adults and children over 50 pounds*—250 mg. every six hours. For severe infections, these dosages may be doubled.

Available in Pulvules®, suspension, drops, and chewable tablets. Ilosone Chewable tablets should be chewed or crushed and swallowed with water.

Additional information available to physicians upon request.
Eli Lilly and Company, Indianapolis, Indiana 46206.

Lilly

600541

California Medicine

Phenylketonuria

Early Detection, Diagnosis and Treatment

GEORGE C. CUNNINGHAM, M.D., *Berkeley*

■ *Phenylketonuria can now be detected during the first few days of life by two reliable mass screening techniques; and its major consequence, severe mental retardation, can be prevented by the early institution of a low phenylalanine diet. Case finding, based on determination of phenylalanine serum levels in newborns before discharge from the hospital, appears to yield an acceptable number of new cases without excessive numbers of false positive or false negative tests at the 4 mg per 100 ml reporting level. Feeding history does not appear to be a major factor in influencing test results.*

In addition to finding cases of phenylketonuria, newborn blood screening has called attention to another group of infants with hyperphenylalaninemia of other causes. The differential diagnosis in such cases is important because the restrictive diet necessary for patients with phenylketonuria might be harmful to others. Such factors as enzymatic immaturity, heterozygote carriers, maternal enzymatic capacities and other amino-acidemic states must be ruled out by thorough examination. Careful observation, investigation and reporting of experience with these patients will help to eliminate some of the present deficiencies in the knowledge of normal and abnormal amino acid metabolism.

PHENYLKETONURIA (PKU) IS AN INHERITED inability to convert the essential amino acid phenylalanine to tyrosine as a result of a lack of the hepatic enzyme *phenylalanine para-hydroxylase*. The failure to form functional enzyme is inherited as an autosomal recessive. The incidence in the general population is one in eight to ten thousand.[33] If untreated, the condition leads to severe mental retardation. The phenylketonuric infant generally has high serum phenylalanine levels (over 8 to 10 mg per 100 ml) soon after birth and, as a result of continued ingestion of phenylalanine-containing protein, the serum phenylalanine will increase to values over 15 mg per 100 ml in a few more days. The urine will sooner or later (2 to 60 days) contain phenylpyruvic acid and other ketoacids which accumulate as the serum phenylalanine rises, and it will turn green upon the addition of ferric chloride. Ortho-

---

From the California State Department of Public Health, Berkeley.

This study was partially supported by Children's Bureau Project: Services and Studies in the Detection of Heritable Diseases in the Newborn.

Submitted 13 April 1966.

Reprint requests to: Bureau of Maternal and Child Health, California State Department of Public Health, 2151 Berkeley Way, Berkeley, California 94704 (Dr. Cunningham).

hydroxyphenylacetic acid can be demonstrated on urine chromatography. Amino acid chromatography of the urine will generally indicate a fairly specific increase in phenylalanine without generalized amino-aciduria. Serum tyrosine levels in the newborn may be normal or high, depending on diet and degree of enzymatic maturity, but after the infant is two weeks of age the levels fall to the low normal ranges. A family history of mental retardation is often obtained and phenylalanine loading tests of the parents will usually have abnormal results. Infants with phenylketonuria should be placed on a specially prepared low phenylalanine diet as soon as possible. It is the early detection of such infants that justifies mass screening programs.

Screening Methods

The first screening test employed to detect PKU was the urine test. Ferric chloride will react with certain ketoacids present in the urine of most phenylketonuric persons to give the urine a green color for a short time. The difficulties in obtaining specimens of fresh urine, the delay in appearance of the abnormal urine products and the intermittency of excretion made this form of testing unreliable as the sole method of case finding.[11,15] Urine testing on older infants is a reasonably reliable and inexpensive method of checking the results of the newborn blood test and its use for this purpose is to be encouraged.

The possibility of early detection became a reality with the development of appropriate methods for the determination of serum phenylalanine. The most widely used screening method is the microbiological inhibition assay of Guthrie and coworkers.[16] This method utilizes a blood specimen collected on special filter paper. A uniform disc is punched out and placed on a plate of bacteriological media which contains beta-2-thienylalanine, a substance inhibitory to growth of the *Bacillus subtilis* organisms inoculated on the plate. If phenylalanine is present in the blood, it diffuses out into the surrounding media and counteracts the inhibition, allowing a halo of growth proportional to the amount of phenylalanine present. By use of appropriate standards, quantitative estimates can be made. More exact determination is possible by the use of the chemical analysis of McCaman and Robins.[35] This test is based on the fact that the fluorescence of the phenylalanine-ninhydrin reaction product can be enhanced by the peptide *L-leucylalanine*. Both of these methods have been effectively employed in large-scale screening programs.

A method developed by La Du and coworkers[29] that is applicable to higher concentrations of phenylalanine is based on the conversion of phenylalanine to the alpha keto acids with snake venom *L amino acid oxidase*. An enol-borate complex is then formed and measured spectrophotometrically. This method may also be used to determine tyrosine. The La Du method is useful for confirmation of high levels but it is of questionable value for screening or monitoring treatment.[31] Other methods have been used in special applications, such as column, paper, and thin layer chromatography, electrophoresis, a laborious decarboxylation method, and other older or less well known methods. These have not yet been extensively applied in screening programs.

Importance of Early Detection

In order to find the small number of affected persons (for example, it is estimated that of the approximately 390,000 babies to be born in California this year, 40 will have phenylketonuria) and to prevent the appreciable financial cost and personal tragedy these infants would present if not treated in time, it is obvious that all infants must be tested. At present there is no other way of case-finding. If high-risk families could be identified, at the cost of one defective phenylketonuric child, testing of these families only would detect approximately 20 per cent of cases. The remaining 80 per cent would be the first affected children in their families.

The first days of life are the appropriate time for testing because ultimate mental performance is related to the age at which therapy is begun.[13,21,28] Knox[27] reviewed results of treatment in relation to age at which treatment was begun. Four hundred forty-six untreated patients were compared with 44 patients treated after age three years and 43 patients treated before three years of age. Those treated before three years of age were subdivided into a group treated before the median age of 16 months and a group treated after. There was a statistically significant increase in final intelligence quotient with early treatment ($P < .01$). Knox estimated at least a five point loss of intelligence quotient with each 10 weeks that treatment was delayed. However, there is reason to believe that intelligence quotient loss is more rapid in the first few weeks of life. Kang and coworkers[23] reported confirming data on 43 infants

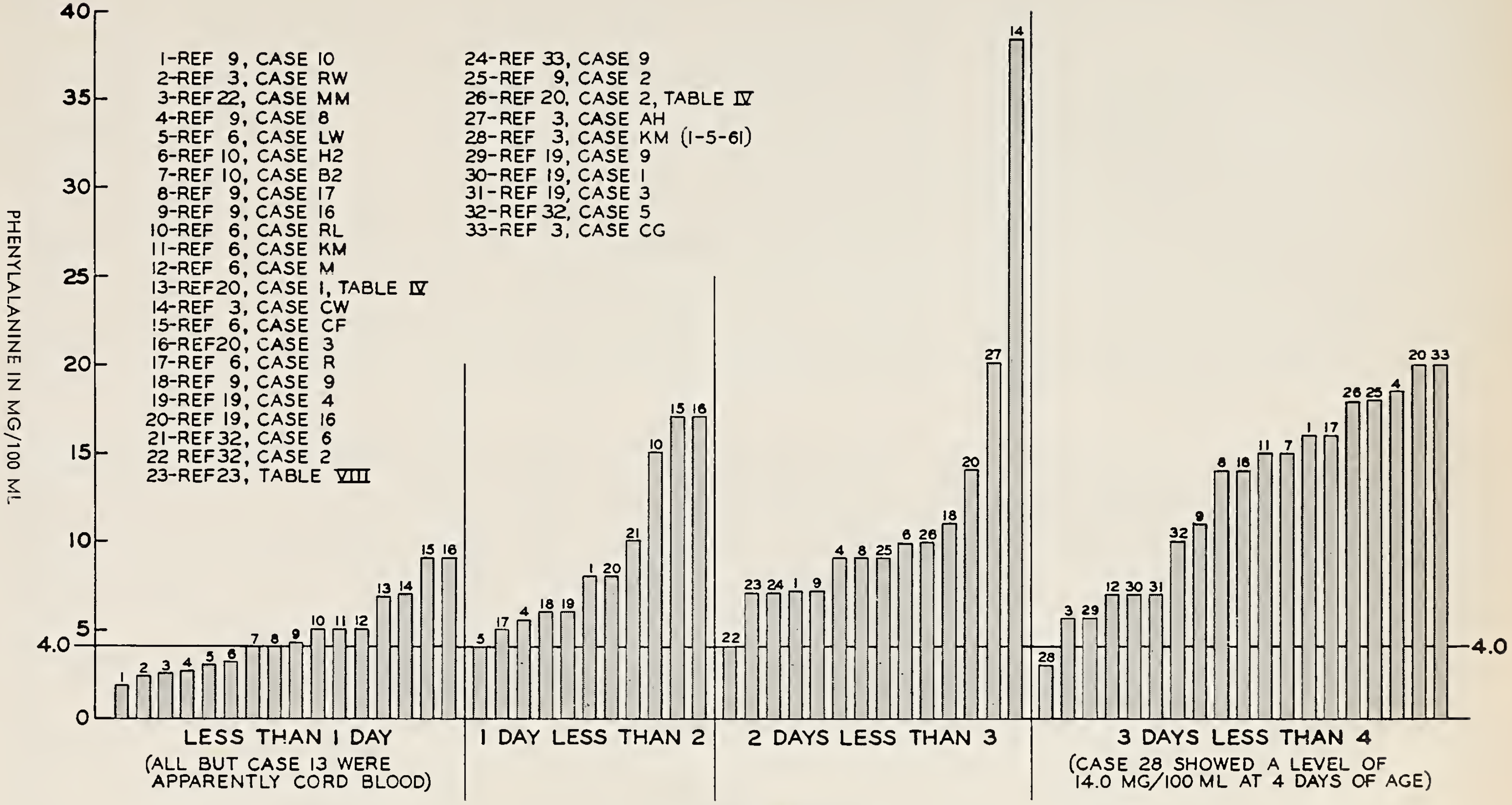


Chart 1.—Serum test results of 33 phenylketonuric infants tested before four days of age.

Errata: In Case 9, above, the reference number should be 18 instead of 20; in Case 25, the reference should be to 19 instead of 9.

in whom the condition was diagnosed at from two to five weeks of age, suggesting that a delay of only 3.6 weeks was associated with developmental achievement significantly less than normal. In short, from the data currently available there is no safe period during which diet can be withheld without fear of resulting brain damage. Moreover, Allen[2] stated that the prevention or reversal of central nervous system toxicity seemed to occur on dietary therapy only if the infant was less than one month of age at the time of diagnosis. It is therefore urgent that the diagnosis be made as soon as possible. The logistics of assuring reasonably complete testing, and the necessity for early diagnosis, dictate that the hospital nursery be selected as the only practical point where these objectives can be attained.

Timing of Test

Most screening programs specify that the infant be tested before leaving the newborn nursery. Because of the assumption that protein feeding is required to elevate serum phenylalanine, some investigators have voiced concern that the diagnosis may be missed in some cases due to early discharge of newborn infants. Review of the evidence, however, suggests newborn screening by serum testing at the time of discharge will result in adequate case-finding. Supporting data come from (1) results of follow-up tests; (2) data on serum level versus age; (3) reports of missed cases; and (4) results of a California pilot study.

In Massachusetts the initial test was taken on the average at 3.9 days of life. The follow-up test obtained at four to six weeks of age has revealed only one missed case in over 335,177 infants tested as of 28 February 1966, if the recommended level of 4 mg per 100 ml is used.[34] In Ohio 44,984 follow-up tests revealed only one additional case which might be PKU.[14] Correspondence with officials in most of the other states having follow-up programs has failed to reveal additional unreported missed cases. There would seem to be little question of the efficacy of tests taken beyond the third day of life. The period of concern then is the first three days.

When serum levels determined during these first three days in known cases of phenylketonuria are compared with normal levels, the groups are clearly separated even at two days of life (Chart 1). The fact that affected infants with little phenylalanine ingestion have had serum elevations quite early is emphasized by the fact that several breast-fed infants were included.

Furthermore, a search for missed cases has revealed a total of seven instances where the newborn test was negative (Table 1). Patient No. 1 would not have been missed by current standards since the infant had two inhibition assay tests indicating phenylalanine content of 4 mg per 100 ml or over. Infant No. 2 was detected recently at the current 4 mg per 100 ml reading level. In Rhode Island it is reported two patients were missed on screening. In one of these (No. 3 in Table 1) the failure may have been due to a technical error since the original filter paper sample initially reported as showing 2 mg per 100 ml was found on retesting to show more than 20 mg per 100 ml on duplicate determinations. In the other case (No. 4) the diagnosis was apparently brought to

TABLE 1.—*Summary of Phenylketonuria Cases Missed In Newborn Screening Programs*

Case and State	*Reference*	*Age in Days Initial Test*	*Duration* of Feeding*	*Initial Result† mg/100 ml*	*Age in Days Repeat Tests*	*Repeat Results mg/100 ml*	*Comments*
No. 1 (Mass.)	33	3	2 days	4-6 (I)	62	10.5 (F)	Not a missed case by current standards.
No. 2 (Mass.)	34	2	1 day	2-4 (I)	15	>50 (I)	PKU
No. 3 (R. I.)	30	3	60 hr.	2 (I)	28	>20 (I)	Retesting original sample, two of three spots read over 20 mg/100 ml.
No. 4 (R. I.)	30	2	36 hr.	<2 (I)	63 75	10 (I) 14.7 (S) 12-20 (I)	PKU
No. 5 (Ohio)	14	4	?	<2 (I)	30 62	6 (I) 10.5 (F)	Diagnosis of PKU not conclusive.
No. 6 (Calif.)	26	2	24 hr.	3.9 (F)	63	35.0 (F)	PKU
No. 7 (Oregon)	7	3	42 hr.	<4 (I)	63	>20 (I)	PKU

---

*All infants shown in the table were formula fed with the possible exception of case No. 5 for whom data are not available.

†Type of test is indicated by (F) fluorometric, (I) inhibition assay, (S) spectrophotometric.

light by a loading test. Patient No. 5 was not reported in sufficient detail to confirm or deny the diagnosis of PKU, but the initial test was on the fourth day of life and showed less than 2 mg per 100 ml; on the 30th day it was 6 mg per 100 ml and on the 62nd day 10.5 mg. The child was placed on a diet at this point. Patient No. 6 had an initial test at 46 hours of age, after 24 hours of formula feeding, showing 3.9 mg per 100 ml.[26] Subsequent to a positive ferric chloride test, a repeat serum determination at 63 days of age was 35.0 mg per 100 ml. Diagnostic evaluation then confirmed the diagnosis of PKU. There are, therefore, counting the patient reported from Oregon (No. 7) who had a negative test after 42 hours of feeding, a total of four confirmed missed cases, and two possible missed cases out of a combined total of well over a half million tests of newborns. As to the importance of feeding, it should be noted that in all of these cases there had been a reasonable period of milk ingestion—24 hours or more.

A recent study demonstrated that doubling the phenylalanine load—comparing breast-fed infants with bottle-fed infants—produced only a minor change in mean serum levels over the first three days of age.[26] Loading tests using 100 mg phenylalanine per kg of body weight in normal infants 14 to 32 hours of age, indicated that these infants were able to metabolize appreciable amounts of phenylalanine.[3] Preliminary data using smaller amounts indicate that loads of up to 30 mg per kg of body weight are handled without elevation of serum phenylalanine in infants less than 24 hours of age.[1] Three hours after birth a normal infant born to a phenylketonuric mother showed a serum phenylalanine by inhibition assay determination of over 20 mg per 100 ml. At eight hours it was 20 mg per 100 ml, but by 16 hours the infant's enzymatic activity had reduced the level to the normal range, 2 mg per 100 ml.[12] At 24 hours of age breast feeding was begun but the serum level remained less than 2 mg per 100 ml for the next three days. This phenylketonuric woman produced breast milk containing 6 mg of free phenylalanine per 100 ml and presumably 64 mg per 100 ml of phenylalanine in milk protein. On the other hand, a phenylketonuric infant followed from birth gave values of 6 to 8 mg per 100 ml of serum at eight hours of age, 10 mg per 100 ml at 31 hours of age after only two bottles, 12 to 20 mg per 100 ml at 55 hours of age and over 20 mg by 67 hours of age. Another phenylketonuric infant had 20 mg per 100 ml at two and a half days of age after 48 hours of breast feeding,[12] and a third infant had 11.9 mg per 100 ml (by fluorometric method) after only 26 hours of breast feeding.[26] The contrast in response between infants with enzymatic deficiency and that of normal infants is apparent very shortly after birth and is not much dependent on the amount of phenylalanine ingested. It thus appears that at least by 24 hours of age the screening test has sufficient reliability to justify the testing of newborns at the time of discharge, regardless of feeding history.

Diagnostic Problems

It is important to distinguish between a screening test and a diagnostic test. A screening test merely selects from a large group those individuals who have a high risk of being affected. Not every case of high serum phenylalanine is necessarily a case of phenylketonuria, but every case of high serum phenylalanine represents an individual at high risk and requires a diagnostic evaluation. It is important that a positive screening test be interpreted to the family in light of its true meaning without engendering unwarranted anxiety.

Appreciation of this distinction will indicate the course of action to be followed when a positive screening result—that is, a serum phenylalanine of 4 mg or more per 100 ml—is reported and confirmed on repeat testing. The current consensus of investigators most experienced in this disorder is that dietary treatment should be instituted at the earliest opportunity. There is, therefore, a sense of urgency in making the diagnosis. This must be tempered, however, by the realization that many of the elevations of serum phenylalanine reported are not due to genetic absence of phenylalanine parahydroxylase and by the fact that placing a phenylketonuric infant (and more especially a non-phenylketonuric infant) on the low phenylalanine diet can result in serious consequences,[17,37] including widespread skin rash, failure to thrive, weight loss, listlessness, anorexia, megaloblastic anemia, hypoglycemia, convulsions and death. The physician is faced with the dilemma of the urgent need for institution of the diet versus the real possibility of harm in unnecessary phenylalanine restriction. To resolve this dilemma, knowledge of the differential diagnosis and special testing procedures are required. The points to be considered are the level of phenylalanine and tyrosine and their rates of change in the serum, the presence of phenylalanine and orthohydroxyphenylacetic acid and other metabolites in the urine, the age of the infant, the diet and biochemical and genetic knowledge of the family.

A statement by the Committee on the Handicapped Child of the American Academy of Pediatrics on treatment of phenylketonuria[1] pointed out some of these problems and recommended:

"Because of these and other problems of diagnosis and management, most clinics attempting optimal services to children with PKU utilize a multidisciplinary team. The coordination of pediatric, social work, psychological, nutritional, and nursing skills in such a team, together with the assistance of a qualified biochemical laboratory, facilitates good care of these children as well as studies of possible improvements in diagnosis and treatment. Since many pediatricians complete their training without ever seeing a case, and/or without the opportunity to supervise the care of children with the disorder over a period of time, it is recommended, where possible, that physicians take advantage of centers combining these multidisciplinary skills for assistance in diagnosis, treatment, follow-up care, and study of patients with phenylketonuria."

Differential Diagnosis

There is a group of infants who will have elevation of serum phenylalanine, usually in the range of 6 to 12 mg per 100 ml but occasionally higher, who do not have phenylketonuria. There are a number of possible explanations for hyperphenylalaninemia. Without attempting to consider in detail the differential diagnosis, a few possibilities will be briefly considered in order to indicate the complexities that may be involved.

First, the infant could be a heterozygous carrier. While most heterozygotes have serum values within the normal range, occasionally values are slightly elevated.[3,5,24] Usually the level does not rise more than a few mg per 100 ml with continued milk feeding, and eventually declines. Tyrosine levels have not been reported but would be expected to be low or normal. Urine tests would probably be negative. The incidence of elevated levels in heterozygotes is probably low but remains for future work to determine.

A second possibility is that the infant could be a normal offspring of a heterozygous or homozygous mother.[24] Some of these mothers have serum levels of 10 to 15 mg per 100 ml in the case of carriers and over 20 mg per 100 ml if they are themselves phenylketonuric. Such a possibility could be ruled out by checking cord blood or mother's blood as soon as possible after delivery. The infant's level will soon decline, as will that of the heterozygous mother. The infant's urine will probably be negative if the mother is the carrier and the infant unaffected, but may be positive if the mother is affected (that is, phenylketonuric) and her serum phenylalanine level is high enough.[38]

A third possibility is the delayed maturity of the enzymatic systems involved. Menkes and Avery[36] reported that 25 per cent of premature infants tested in their series had at least one determination of serum phenylalanine above 5 mg per 100 ml. Most of these infants also had elevated serum tyrosine. Based on work by Kenney and Kretchmer[25] and others, this is believed to be due to a transient immaturity or inadequacy of phenylalanine parahydroxylase. This enzyme apparently becomes active in different infants some time during the first few days of life. The capacity of an infant's enzyme systems may be transiently exceeded so that serum levels of phenylalanine over 4 mg per 100 ml may be obtained at four weeks of life when the nursery specimen was normal. True phenylketonuria is usually distinguished by low tyrosines, and by the persistence of the defect. Serial determinations of phenylalanine and tyrosine and examination of the urine for metabolites will frequently be required to resolve the problem.

In addition, there is a variety of hepatic toxins and infections which could conceivably elevate serum phenylalanine, although there is as yet no documentation of such cases. The matter is further complicated by the observation that an infant who had persistent phenylalanine elevation (8 to 10 mg per 100 ml) for one year with negative ferric chloride test, eventually was believed to have PKU because of failure to convert a phenylalanine load to tyrosine.[15] Premature infants represent a special problem and require careful observation and serial determinations before the significance of hyperphenylalaninemia can be determined. Levels as high as 20 mg per 100 ml (by inhibition assay) have been reported for a normal premature baby.[33] Recently criteria for diagnosis and treatment have been suggested by Berry and coworkers.[8] Even with extensive evaluation, the differentiation of the hyperphenylalaninemia of PKU associated with mental retardation from other causes of high serum phenylalanine may not be definitely resolved, since this is a large area needing further investigation.

REFERENCES

1. Ackerman, B. D., and Nelson, T. L.: Phenylalanine loading in newborn infants, Western Society for Pediatric Research, Abstract 41, 13th annual meeting, November 1965.

2. Allen, R. J.: Neurological abnormalities in phenylketonuria biochemically unrelated to phenylalanine intoxication, Am. J. Dis. Child., 104:487-488, November 1965.

3. Allen, R. J., Heffelfinger, J. C., Masotti, R. E., and U Tsau, M.: Phenylalanine hydroxylase activity in newborn infants. I. Relation to the appearance of metabolites in blood and urine in normal and enzyme deficient states. II. Relation to the clinical diagnosis of phenylketonuria, Pediatrics, 33:512-525, April 1964.

4. A.M.A. Statement on treatment of phenylketonuria, Committee on the Handicapped Child, Edw. Davens, Chairman, American Academy of Pediatrics, Pediatrics, 35:501-503, March 1965.

5. Anderson, J. A., Fisch, R., Miller, E., and Doeden, D.: Atypical phenylketonuric heterozygote, J. Pediat., 68:351-360, March 1966.

6. Armstrong, M. D., Centerwall, W. R., Horner, F. A., Low, N. L., and Weil, W. B., Jr.: "The development of biochemical abnormalities in phenylketonuric infants," in Chemical Pathology of the Nervous System, Folch-Pi, J., ed., Pergamon Press, New York, 1961.

7. Ashley, C. G., and Brandon, G. R.: Phenylketonuria detection, letter to the Editor, Pediatrics, 36:454-455, September 1965.

8. Berry, H. K., Sutherland, B., and Umbarger, B.: Diagnosis and Treatment: Interpretation of results of blood screening studies for detection of phenylketonuria, Pediatrics, 37:102-106, January 1966.

9. Berry, H. K., Umbarger, B., and Sutherland, B.: Testing of newborn siblings in phenylketonuric families, J.A.M.A., 189:641-642, 24 August 1964.

10 Centerwall, W. R., Centerwall, S. A., Acosta, P. B., Chinnock, R. F., Armon, V., and Mann, L. B.: Phenylketonuria. I. Dietary management. II. Results of treatment, J. Pediat., 59:93-101, 102-118, July 1961.

11. Centerwall, W. R., Chinnock, R. F., and Pusavat, A.: Phenylketonuria: Screening programs and testing methods, Am. J. Pub. H., 50:1667-1677, November 1960.

12. Coffelt, R. W.: Personal communication, 15 March 1966.

13. Conference on phenylketonuria, A. A. Moncrieff, Chairman: Treatment of phenylketonuria, Brit. Med. J., pp. 1691-1697, 29 June 1963.

14. Croft, C. C.: Screening for phenylketonuria in Ohio, presented at annual meeting, conference of state and provincial public health laboratory directors, Chicago, Illinois, 17 October 1965.

15. Efron, Mary L., and MacCready, R. A.: Phenylketonuric families, J.A.M.A., 191:119-120, 1 February 1965.

16. Guthrie, R., and Susi, A.: A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants, Pediatrics, 32:338-343, September 1963.

17. Holt, K. S.: Difficulties and dangers in the management of phenylketonuria, Acta Paediat., 52:417-424, July 1963.

18. Horner, F. A., and Streamer, C. W.: Phenylketonuria treated from earliest infancy, a report of three cases, Am. J. Dis. Child., 97:345-347, March 1959.

19. Hsia, D. Y., Berman, J. L., and Slatis, H. M.: Screening newborn infants for phenylketonuria, J.A.M.A., 188:203-206, 20 April 1964.

20. Hsia, D. Y., Litwack, M., O'Flynn, M., and Jakovcic, S.: Serum phenylalanine and tyrosine levels in the newborn infant, N. Engl. J. Med., 267:1067-1070, 22 November 1962.

21. Hsia, D. Y., Rowley, W., and Raskin, N. J.: Clinical management of phenylketonuria, Quarterly Bull. N.W.U. Med. School, 36:25-32, 1962.

22. Hudson, F. P., Dickinson, R. A., and Ireland, J. T.: Experiences in the detection and treatment of phenylketonuria, Pediatrics, 31:47-57, January 1963.

23. Kang, E. S., Kennedy, J. L., Jr., Gates, L., Burwash, I., and McKinnon, A.: Clinical observations in phenylketonuria, Pediatrics, 35:932-943, June 1965.

24. Kang, E. S., and Paine, R. S.: Elevation of plasma phenylalanine levels during pregnancies of women heterozygous for phenylketonuria, J. Pediat., 63:283-289, August 1963.

25. Kenney, F. T., and Kretchmer, N.: Hepatic metabolism of phenylalanine during development, J. Clin. Invest., 38:2189-2195, December 1959.

26. Kleinman, D. S., Twiss, S., and Day, R. W.: Some factors affecting McCaman-Robins test results in screening newborns for PKU (in press).

27. Knox, W. E.: An evaluation of the treatment of phenylketonuria with diets low in phenylalanine, Pediatrics, 26:1-11, July 1960.

28. Koch, R., Fishler, K., Schild, S., and Ragsdale, N.: Clinical aspects of phenylketonuria, Mental Retardation, 2:47-54, February 1964.

29. La Du, B. N., Howell, R. R., Michael, P. J., and Sober, E. K.: A quantitative micromethod for the determination of phenylalanine and tyrosine in blood and its application in the diagnosis of phenylketonuria in infants, Pediatrics, 31:39-46, January 1963.

30. Lundgren, R. G.: Personal communication to B. D. Ackerman, California College of Medicine, 30 September 1965.

31. Lundgren, R. G.: Personal communication, 11 January 1966.

32. Lundgren, R. G., Kugel, R. B., and Corrigan, F: Phenylketonuria—a progress report, R. I. Med. J., 48: 429-430, August 1965.

33. MacCready, R. A., and Hussey, M. G.: Newborn phenylketonuria detection program in Massachusetts, Am. J. Pub. H., 54:2075-2081, December 1964.

34. Massachusetts Dept. of Public Health: Personal communication, 11 March 1966.

35. McCaman, M. W., and Robins, E.: Fluorometric method for the determination of phenylalanine in serum, J. of Lab. & Clin. Med., 59:885-890, May 1962.

36. Menkes, J. H., and Avery, M. E.: The metabolism of phenylalanine and tyrosine in the premature infant, Bull. Johns Hopkins Hosp., 113:301-319, 1963.

37. Umbarger, B., Berry, H. K., and Sutherland, B. S.: Advances in the management of patients with phenylketonuria, J.A.M.A., 193:784-791, 6 September 1965.

38. Woolf, L. I., Ounsted, C., Lee, D., Humphrey, M., Cheshire, N. M., and Steed, G. R.: Atypical phenylketonuria in sisters with normal offspring, Lancet, 2:464-465, August 1961.

Cancer of the Larynx

Results of Surgical and Radiological Treatment in One Institution

L. HENRY GARLAND, M.B., M.D., (HON.), *San Francisco*

■ *Of 67 consecutive patients with cancer of the larynx seen at the San Francisco General Hospital from 1948-1960 inclusive, 25 were treated primarily by radical radiotherapy and 31 by radical surgical operation. Of the 25 treated by radiotherapy (with surgery for failure in three instances) 13 apparently had arrest of disease and nine of these remained cured five or more years. Four died of intercurrent disease.*

Of the 31 treated primarily by radical operation (with subsequent radiation for surgical failure in 11 patients), 13 had potential arrest of disease and seven of the 13 remained cured for five or more years. Six died of intercurrent disease before the lapse of five years, three of them within four weeks of radical operation.

Radical radiotherapy of laryngeal cancer produced results superior to those of radical surgery in patients seen and treated during the period under review in this hospital.

THE FOLLOWING is a report on the results of treatment of cancer of the larynx at the San Francisco General Hospital during the years 1948-1960 inclusive. Survival data are for five or more years. To the best of our knowledge all primary previously untreated cases of laryngeal cancer seen during that period are included. The San Francisco Hospital is an institution for city indigents. Many of the patients are or were accordingly in less than ideal physical and nutritional status. Results in patients seen in private practice tend to be better because of less advanced disease, and greater ability to tolerate vigorous therapy.[1,2,3,4]

All patients had microscopic verification of the tumor; most were seen by the Tumor Board; all were followed up to date.

The total number of previously untreated patients was 67, of whom 36 received primarily radiotherapy and 31 primarily surgical therapy.

Radiotherapy

The 36 patients treated primarily by radiotherapy were in various stages of the disease, localized to advanced.

There were four in whom treatment could not be completed because of advanced age, advanced disease or (in one case) refusal to accept more than six treatments.

Seven patients could be given only palliative treatment on account of advanced disease or debility (palliative meaning a tumor dose of less than 4,500 rads in six weeks).

Twenty-five patients were given radical treatment with intent to cure (4,500-6,500 orthovoltage rads in four to eight weeks, to fields ranging from 5 to 8 cm in average diameter).

In none of the patients who received partial or palliative treatment was the disease arrested.

From the Department of Radiology, University of California, San Francisco General Hospital, San Francisco.

Submitted 18 January 1966.

Reprint requests to: 450 Sutter Street, San Francisco, California 94108.

TABLE 1.—*Results with Radiotherapy Alone: 33 Cases (All Stages)*

(Palliative (less than 4,500 rads in 6 weeks), 7 cases; radical (4,500-6,500 rads in 4 to 8 weeks), 22 cases; incomplete (less than 2,500 rads in 4 weeks), 4 cases).

	Clinically Cured Five or More Years	*Cancer Arrested But Dead of Intercurrent Disease*	*Dead of Cancer*
Palliative	0	0	7
Radical	8	4	10

Of the 22 patients treated by radical radiotherapy alone, 12 had arrest of disease but four died of intercurrent disease before the five-year period had elapsed—a common occurrence in laryngeal cancer since so many of the patients are elderly. Ten died with cancer. Eight apparently are cured.

These findings are summarized in Table 1.

In addition to the patients treated by radical radiotherapy alone, there were three treated by radical radiotherapy plus subsequent surgical operation for persistent disease. One of these was cured; two died of cancer. Table 2 summarizes data on these three patients.

In all, there were 25 patients treated by radical radiotherapy (three of them with postradiation surgical operation), and nine of them had clinical cure for five or more years. Two of the nine had been treated by hard x-rays (telecobalt), the rest by conventional x-rays (orthovoltage).

Radical Surgical Therapy

Thirty-one patients were treated by radical surgical operation. Most of them had Stage I or II disease, but a few had palpable nodes at time of treatment. Of the 31 patients, 20 were treated by surgical operation alone, and 11 by operation plus postoperative radiotherapy for persistent or recurrent disease.

Of the 20 treated by radical operation alone, 12 had potential arrest of cancer, but five died of intercurrent disease before the five-year period elapsed. Eight died of cancer. Three of the five with potential arrest died within four weeks of the operation and death might be classified as surgical mortality. One of the seven patients had arrest for four years, then had recurrence in the fifth and died of cancer in that year. These results are summarized in Table 3.

Of the 11 patients with persistent or recurrent disease after radical operation and then treated by radiotherapy only, one was clinically cured for five or more years. Ten died of cancer.

The site of primary tumor differed somewhat in the two groups of cases (surgical and radiological), and the anatomic extent of disease was on average more advanced in the radiological group. The primary site in the two groups, excluding the four patients who received only token therapy, was as follows:

Site	*Radiation*	*Operation*
Supraglottic	19	14
Glottic	13	16
Infraglottic	0	1
Total	32	31

The results of radical operation and of radical radiotherapy when each is used alone are summarized in Table 4. While the cases were not identical in anatomic extent of disease, the lesion was squamous cell cancer in all cases and the patients were all treated in one hospital by one method or the other during the same 13-year period. In the surgically treated patients the lesions were on av-

TABLE 2.—*Data on Three Patients with Radiotherapy and Subsequent Radical Operation*

Patient and Disease	*Radiotherapy*	*Operation*
Man 65—Supraglottic, Stage III	6,500 rads in 60 days, July and August 1950, Residual tumor March 1951	April 1951 Died June 1951 Residual tumor and bronchopneumonia
Man 55—Supraglottic, Stage II	5,100 rads in 39 days, August and September 1948, Residual tumor October 1950	November 1950 Living and well, January 1966
Man 45—Supraglottic, Stage III (pretreatment tracheostomy)	5,300 rads in 27 days, November 1948, Residual tumor March 1949	April 1949 Died November 1950 Residual tumor

erage less extensive than in those treated by radiation, and the survival rates in that group might therefore have been expected to be better. Eight of 22 patients treated by radiotherapy alone and six of 20 who were treated by surgical operation alone had arrest of disease.

When one considers the entire group of radically treated patients, it is noted that nine of 25 patients treated primarily by radiotherapy (with subsequent operation for failure in three cases) and seven of 31 treated primarily by radical operation (with subsequent radiation for failures in 11 cases) were clinically cured.

Comment

As indicated in the opening paragraphs, the results of treatment of cancer of the larynx in a County Hospital tend to be less favorable than those in a private hospital or in private office practice. Patients in the former institution tend to have more advanced disease and to be in poorer general health. Nevertheless, it is believed that the data recorded herewith continue to support the contention that radiotherapy has an established and useful place in the treatment of this disease.

The patients cured by radiotherapy have the advantage of salvage of voice and certain other functions.

Major complications of radiotherapy, such as disabling laryngeal edema and chondronecrosis, were not observed in this series. However, in three patients treated elsewhere and referred to this hospital for terminal care during the years in question, such undesirable radiation reactions were recorded and have been discussed elsewhere.[1]

REFERENCES

1. Garland, L. H.: The current status of radiotherapy in carcinoma laryngis, Ann. Otol., Rhin. & Laryng., 73: 488, 1964.

2. Goldman, J. L., Silvertone, S. M., Rosin, H. D., Cheren, R. V., Zak, F. G.: Combined radiation and surgical therapy for cancer of the larynx, Laryngoscope, 74:1111, 1964.

3. Pollack, R. S.: Indications for operation in laryngeal cancer, Calif. Med., 95:115, 1961.

4. Sheline, G. E., and Stone R. S.: Carcinoma of the larynx, Ann. Otol., Rhin. & Laryng., 67:1066, 1958.

TABLE 3.—*Results in 20 Patients (mostly with Stage I or II Disease) Treated by Radical Operation Alone*

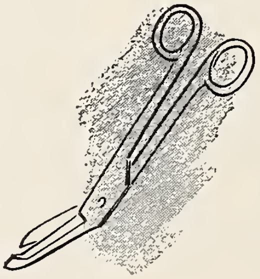
Clinically Cured Five or More Years	*Arrest but Dead of Other Cause*	*Dead of or with Cancer*
6	5*	9

*Three died within four weeks of operation.

TABLE 4.—*Survival (5 years) by Radical Treatment**

Site	*Radiation*	*Surgery*
	(Number of Patients)	*(Number of Patients)*
Supraglottic	Two of 10	Three of 8
Glottic	Six of 12	Four of 11
Infraglottic	Zero of 0	Zero of 1
Total	Eight of 22	Six of 20

*Radiotherapy alone or surgical operation alone. Three additional patients had post-radiation operation, one survivor. Eleven additional patients had post-operation radiation, one survivor.



RHEUMATIC FEVER

Summary of a Rheumatic Fever Workshop on Various Aspects of the Disease

DONALD C. FYLER, M.D., FORREST H. ADAMS, M.D., CHARLES F. PAIT, M.D.
GEORGE C. GRIFFITH, M.D., *Los Angeles*

■ *While rheumatic fever is becoming an uncommon disease in all parts of the United States, it still exists in all areas including Southern California. The disease is sufficiently common in Los Angeles County to warrant organized programs of control aimed particularly at careful follow-up, accurate case reporting, secondary prophylaxis and primary prevention.*

In April of 1965 a Rheumatic Fever Workshop, in which local, national and state experts in rheumatic fever participated, reviewed the status of the rheumatic fever programs in Los Angeles County. Guidelines for future organization for the control of rheumatic fever were developed and presented.

In April 1965, 15 Los Angeles physicians with a wide range of experience and organizational affiliation relating to rheumatic fever and rheumatic heart disease met at the Hollyhock House in Los Angeles. Invited state and national participants were present (see Appendix). The purpose of this meeting was to review existing programs for rheumatic fever control and to recommend guidelines for community efforts in controlling this disease.

The purpose of this communication is to report the consensus of these discussions.

Previously, local committees have usually centered their discussions around the difficult question of the prevalence of rheumatic fever in Southern California. There have been no available prevalence data other than through the collection of opinions. It has usually been concluded that there is insufficient rheumatic fever to constitute a significant problem. Nonetheless, the thought has persisted that without adequate local prevalence data one could not be certain. Locally pediatricians see active rheumatic fever, internists see rheumatic heart disease and thoracic surgeons are correcting rheumatic valvular deformities. The widely held concept that these patients do not acquire their primary attack of rheumatic fever in Southern California is satisfying in a Chamber of Commerce sense, but does not reduce our community's responsibility or expense on account of these patients. In addition, the upsurge of national interest in primary prevention of rheumatic fever requires serious reconsideration of local community programs. If primary prevention of rheumatic fever can be demonstrated to be more than a theo-

---

The workshop here reported upon was sponsored by the Heart Disease Control Program, U.S.P.H.S., American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, and Los Angeles County Heart Association. The recommendations of this report do not necessarily reflect the policies of the sponsoring agencies.

Submitted 15 November 1965.

Reprint requests to: Department of Cardiology, Children's Hospital of Los Angeles, 4614 Sunset Boulevard, Los Angeles, California 90027 (Dr. Fyler).

retical possibility, community programs to afford our citizens this benefit will be needed. These considerations led to the formation of the Rheumatic Fever Workshop.

Present Programs

The existing programs for rheumatic fever in Los Angeles are fragmentary and overlapping. The Los Angeles County Health Department administers five children's cardiac diagnostic clinics primarily for the detection of heart disease and also tabulates reports of cases of active rheumatic fever. The Los Angeles County Heart Association has a limited secondary prophylaxis program. Many school systems supply home teachers for children with rheumatic fever, perform routine school physical examinations and refer diagnostic problems to the Parent-Teacher Association clinics or to other clinics. The Crippled Children Services can provide medical financing for diagnosing and treating financially eligible patients under age 21, including the costs of secondary prophylaxis. The Aid to Needy Children Program and the Outside Medical Relief Program also can provide prophylactic medication. There is no organized follow-up of persons who have had rheumatic fever in the County. There is no vocational rehabilitation program per se for adults with rheumatic heart disease. Public health nursing and social service time devoted to patients with rheumatic fever or rheumatic heart disease is negligible.

Prevalence

It is difficult to determine the prevalence of rheumatic fever in Los Angeles County. Although this is a legally reportable disease, it can be readily demonstrated that only a fraction of the total number of cases is reported to the Public Health Department. Those agencies with an interest in rheumatic fever collect some prevalence data, but there is no means of eliminating duplication between agencies and under many circumstances the original diagnosis of rheumatic fever is open to question.

Propp[2] reviewed the charts of patients with diagnosis of rheumatic fever in 1962 in five large Los Angeles hospitals and found 33 cases which were acceptable by utilizing Jones'[1] criteria. Since the use of Jones' criteria seemed to be the community pattern, he then tabulated the medical record room statistics for 15 hospitals with over 200 beds and found 67 additional patients listed. Propp concluded that there was a minimum of 100 episodes of acute rheumatic fever in Los Angeles County in 1962. Reports to the Health Department from all sources totaled 39 for the same period.

In preparation for the Rheumatic Fever Workshop, statistics from six large hospital record rooms were tabulated for 1964. Forty-eight instances of acute rheumatic fever were noted. This figure tends to confirm Propp's conclusion.

For 1964 the Los Angeles Crippled Children Services offered diagnostic services to 1,370 children because of possible rheumatic fever. Fifty-eight of them were accepted for treatment or continued prophylaxis.

The seven Parent-Teacher Association clinics reported seeing 24 children with a history of rheumatic fever and 36 children with rheumatic heart disease in 1963-64.

The Los Angeles City Unified District School physicians examined 273,000 children in 1963-64. Of these 131 were referred for further examination for possible rheumatic fever or rheumatic heart disease. Fifty-five were considered to have had rheumatic fever and 16 were considered possibly to have had rheumatic fever.

School districts accounting for approximately 55 per cent of school children in Los Angeles County provided home teachers for 122 students on account of rheumatic fever in 1963-64. The diagnosis in those cases was unconfirmed.

In 1963-64 physicians at Los Angeles City and County Health Department clinics diagnosed rheumatic fever or rheumatic heart disease in 13 children.

Deaths attributed to acute rheumatic fever in Los Angeles County occur at a frequency rate not greatly different from that in other large United States population areas.[2] It is considered that these data are not precise since they are based on death certificates.

One would expect that prevalence data referable to rheumatic fever in Southern California would be available from insurance companies, from prepaid medical insurance programs, from university student medical records, from nearby counties or from the Los Angeles Heart Association. Reliable data were not available.

It was concluded that a minimum of 100 patients with active rheumatic fever are seen by physicians in Los Angeles each year.

Need

The consensus of the workshop was: *There is good evidence that there is a problem with streptococcal disease and its sequelae—particularly rheumatic fever and rheumatic heart disease —in Los Angeles County.*

Rheumatic fever and rheumatic heart disease do exist in Los Angeles. While precise prevalence data are desirable to gauge the extent of program planning, the precise prevalence need not be determined before proceeding with efforts to control this disease. Since rheumatic fever is the direct sequelae of group A streptococcal infection, obvious avenues for scientific attack are open. That the disease is uncommon does not preclude the possibility of reducing its incidence or prevalence through better management of the primary streptococcal infection, and through controlled secondary prophylaxis in the identified rheumatic individual.

Nowadays rheumatic fever is an uncommon disease in all areas of the United States and is a small part of the over-all community concern with heart disease. Nonetheless, rheumatic fever remains a significant disease in childhood ranking at least as high in incidence as cystic fibrosis, childhood leukemia or rheumatoid arthritis in Los Angeles County. In contrast to these diseases, the hope for benefit from medical supervision is good but the disease is traditionally less favored among those for which money is raised.

The estimated loss of income and the estimated community costs as a consequence of a single patient with rheumatic fever and rheumatic heart disease are staggering.[3]

Guidelines for Program Development

In the approach to control of streptococcal infection and its sequelae in Los Angeles the workshop developed the following principles to be used as guidelines:

Physician Education: *There is need for grass roots education of the medical profession regarding the significance of streptococcal infection and its sequelae.*

While physicians in Los Angeles show commendable precision in the diagnosis of acute rheumatic fever, over-diagnosis does occur. Underdiagnosis was not stressed as a significant problem. The delabeling of cases in which rheumatic fever is incorrectly diagnosed has been demonstrated to be a major benefit of organized rheumatic fever programs elsewhere.

The insufficient use of antibiotic therapy for streptococcal sore throat may be followed by acute rheumatic fever. The causal relationships of streptococcal sore throat to rheumatic fever and to acute glomerulonephritis are established. These documented facts offer a legitimate opportunity to prevent these diseases. The need for imaginative means to bring these facts to the physician and especially to the medical student was emphasized. The mere distribution of pamphlets and posters is to be deplored and results only in cluttered wastebaskets.

Coordination of Present Programs: *There should be close coordination of the various agencies presently engaged in managing the complications of streptococcal infection.*

The overlapping and uncoordinated programs, both public and private, managing patients with rheumatic fever and rheumatic heart disease should be brought together and means found to prevent interagency competition and duplication. The remarkable confusion, duplication and competition that exist in our community are wasteful and not beneficial to the patient. The Heart Association as a volunteer agency can best serve to bring all interested parties together.

Central Collection of Data and Follow-up: *Methods should be established for a central collection of data pertinent to the extent of rheumatic fever and rheumatic heart disease. In the community's interest adequate follow-up should be maintained.*

Without adequate data collection, it is impossible to plan appropriately for the management of this disease. Surveys of incidence and prevalence of rheumatic fever and rheumatic heart disease should be encouraged. Organizational means to insure flow of adequate data should be sought. If the incidence of rheumatic fever can be proved to be lower in Los Angeles than it is in other American cities, this would be a fact of some scientific importance.

There is no significant organized follow-up of known rheumatic patients in Los Angeles County. While the private physician or hospital may perform faultlessly, in our mobile community, the loss to follow-up of an identified rheumatic patient as a consequence of changing residence is a problem. Centralized data collection will uncover the patient lost to follow-up, and public health nursing can then facilitate the return of the patient to appropriate medical management. The family physician can then be assured of the return of the patient for continued care.

The recurrence of rheumatic fever because of lapse of prophylaxis represents a financial drain on the community which will be more than offset by the costs of accurate follow-up. Further, no factual data regarding the natural history of rheumatic fever in Los Angeles can be accumulated without such follow-up data.

Secondary Prophylaxis: *The Los Angeles County Heart Association should provide free prophylactic medication on physician request to all patients who have had rheumatic fever.*

Means to provide free prophylactic medication to the rheumatic patient should be developed. It is considered that provision of free secondary prophylactic medication for patients in this community should initially be the responsibility of the Los Angeles County Heart Association. Provision of free prophylactic medication should result in accumulation of additional prevalence data since minimal documentation of the need for prophylactic medication would be required.

It is not suggested that such a program should necessarily continue indefinitely; rather it should continue as long as it can be shown to provide worthwhile prevalence data. In other cities this approach to prevalence data collection has been successful.

For some unexplained reason prophylactic medication for the secondary prevention of recurrent streptococcal infection among rheumatic patients in California has been limited to benzathine penicillin tablets. It is considered that there may be cheaper and at least equally effective means of prophylaxis. While it is clear that monthly injections of benzathine penicillin provide the greatest degree of protection, oral medication in the form of penicillin G tablets or sulfadiazine has generally proved the most practical.

Primary Prevention of Rheumatic Fever: *The possible primary prevention of rheumatic fever in Los Angeles County poses great problems. Efforts in this direction should be confined to pilot studies and physician education programs.*

The exciting thought of virtually complete eradication of rheumatic fever through a highly organized community attack on streptococcal infection must be tempered by the cost and by the fact that it is not yet known whether such programs are effective. The complicated problems that go with such a program in our widespread metropolitan area should not be underestimated. The experience of other large cities in managing this question should be recognized and continually reevaluated. We are fortunate in having a highly organized and effective streptococcal identification program nearby in Orange County and should be able to draw upon that experiment for guidance. For the present, efforts toward primary prevention in the Los Angeles area should be confined to pilot studies in a localized area of the county.

Local Determination: *The Los Angeles rheumatic fever problem will have to be solved by programs designed for our particular community circumstances.*

Since the problem of rheumatic fever and rheumatic heart disease involves many public and many private agencies which are organized in different fashion from city to city, it is necessary to tailor a rheumatic fever program to the specific local circumstances. Programs which are effective elsewhere would not necessarily be as effective in Los Angeles. The approach to this problem should be methodical, empirical and practical and continually readjusted to the measured extent of the problem. Present evidence suggests that a relatively modest program for Los Angeles might be quite adequate.

Vocational Rehabilitation: *Vocational rehabilitation programs designed for the adult with rheumatic heart disease should be developed.*

There is virtually no program for the rehabilitation of the adult with rheumatic heart disease in our County. It is unreasonable to expect that these people should perform no work or exist as community beneficiaries. The possibility that these people can work despite artificial valve replacement must not be overlooked and as experience accumulates it is expected these individuals will be able to perform in gainful employment.

Research and Training: *Basic research in streptococcal infection and its sequelae should be strengthened.*

Basic research in the sequelae of streptococcal infections is virtually nonexistent in Los Angeles and should be encouraged. Enhanced clinical research and development of public health methods will be a natural consequence of an organized community program.

It is to be hoped that some centralization of patient care can be developed which will provide improved opportunities for teaching.

Liaison with Other Cities: *Liaison between Los Angeles and other areas of the United States should be fostered not only to provide transfer of experience and scientific information but to help identify those individuals with rheumatic heart disease who are arriving in this area in significant numbers.*

It is proposed that yearly conferences utilizing a national consultant would provide better contact with other United States centers. The advantages of a repeat rheumatic fever workshop held at three to five yearly intervals are obvious. With an identifiable, formal Los Angeles program one would hope that immigrating patients known to have had rheumatic fever will be referred directly from out-of-state agencies and that adequate care will be a consequence.

Implementation of a Rheumatic Fever Control Program

The following proposals were made for a Los Angeles Rheumatic Fever Control Program:

Advisory Body: *An advisory committee of broad community representation should be established and should meet regularly to maintain communication between organizations and to seek solution to the control of streptococcal sequelae.*

The structure of this board will be less important than the dedication of the individuals involved. Lay and medical persons known for their informed responsibility in community affairs should be selected. The necessity for a small executive group, capable and likely to meet frequently, was emphasized. Such a board should have the potential of integrating present programs, planning the extent of future programs and maintaining running data on the prevalence of streptococcal sequelae, particularly rheumatic fever.

Heart Association: *The Los Angeles County Heart Association as an interested volunteer community agency should function as the catalytic agency to bring the advisory committee together and help carry out its recommendations.*

It was the consensus of opinion based on experience elsewhere and in the past in our own community that a volunteer agency such as the Heart Association has the most potential for developing solutions for the Los Angeles rheumatic fever problem.

Key Physician: *A carefully selected physician from this community should be appointed to carry out the policies of the advisory committee.*

It was suggested that a physician with local roots and knowledge of our diverse community would be in the best position to implement such a program. He would be charged with responsibility for the day-to-day management of the program within the policies established by the advisory committee.

APPENDIX

Participants in the Rheumatic Fever Workshop

NATIONAL

Alfred M. Bennett, M.D.
Director, Congenital Heart Disease
and Special Studies
American Heart Association, New York

Jean-Maurice Poitras, M.D.
Chief, Rheumatic Fever Section
Heart Disease Control Program, USPHS
Washington, D.C.

Richard Propp, M.D.
Fellow in Hematology
Albany Medical College of Union University
Albany, New York

Lewis W. Wannamaker, M.D.
Professor of Medicine
Department of Pediatrics
University of Minneapolis Medical School
Minneapolis, Minnesota

Milton Saslaw, M.D.
Director, Division of Research and Epidemiology
Dade County Department of Public Health
Florida

Alan C. Siegel, M.D.
Assistant Professor of Pediatrics
Northwestern University School of Medicine
Chicago, Illinois

CALIFORNIA

Rene Bine, Jr., M.D.
Representative of California Heart Association
San Francisco

Nemat Borhani, M.D.
Director, Bureau of Chronic Diseases
State Department of Public Health
Berkeley

Arthur Feinfield, M.D.
President, California Heart Association
Sherman Oaks

Charles R. Gardipee, M.D.
Chief, Crippled Children Services
State Department of Public Health
Sacramento

Edward L. Russell, M.D.
Health Officer, Orange County
Health Department, Santa Ana

Richard A. Young, M.D.
Chief, Bureau of Vocational Rehabilitation
Sacramento

LOS ANGELES

Forrest H. Adams, M.D.
Professor of Pediatrics
UCLA Center for the Health Sciences

Alonzo Cass, M.D.
Senior Public Health Physician
L. A. County Health Department

John M. Chapman, M.D.
Professor of Preventive Medicine
and Public Health
UCLA Center for the Health Sciences
Chairman, Community Services
Committee, Los Angeles County
Heart Association

Eliot Corday, M.D.
President, American College of Cardiology
Representative, L. A. County Medical Association

Sim P. Dimitroff, M.D.
Cardiologist
Associate Clinical Professor of Medicine
USC School of Medicine

Donald C. Fyler, M.D.
Associate Professor of Pediatrics
USC School of Medicine

George C. Griffith, M.D.
Emeritus Professor of Medicine
USC School of Medicine

Henry L. Heins, Jr., M.D.
Chairman, Rheumatic Fever
Prophylaxis Committee
Los Angeles County Heart Association

Lloyd T. Iseri, M.D.
Coordinator of Cardiovascular
Disease Training
California College of Medicine

Arthur J. Moss, M.D.
Professor, Department of Pediatrics
UCLA Center for the Health Sciences
Chairman, Cardiac Clinics Committee
Los Angeles County Heart Association

Charles F. Pait, M.D.
Director, Bureau of Preventable Diseases
L. A. County Health Department

Phillip E. Rothman, M.D.
Clinical Professor of Pediatrics
USC School of Medicine

Morse Shapiro, M.D.
Chief, L. A. Board of Education &
P.T.A. Cardiac Clinics

STAFF

Michael Dohan, M.D.
Heart Disease Control Officer, USPHS
Division of Chronic Diseases
L. A. County Health Department

Robert Durnin, M.D.
Fellow in Cardiology
Children's Hospital, Los Angeles

Chauncey A. Alexander
Executive Director, Los Angeles
County Heart Association

Lee Horovitz
Program Director, Los Angeles
County Heart Association

Kenneth McClain
Program Associate, Los Angeles
County Heart Association

Miss Ruth Morse
Associate Executive Director
California Heart Association

REFERENCES

1. Jones, T. D.: Diagnosis of rheumatic fever, J.A.M.A., 126:481, 1944.

2. Propp, R.: Acute rheumatic fever in Los Angeles County, Calif. Med., 103:334-336, November 1965.

3. Saslaw, M. S., Vieta, A., and Myerburg, R. J.: Cost of rheumatic fever and of its prevention, Am. J. Pub. Health, 55:429, March 1965.

Group Psychotherapy With Adolescents

JOSEPH D. TEICHER, M.D., *Los Angeles*

■ *In working in a large general hospital with groups of disturbed adolescent patients from economically and emotionally deprived walks of life, therapists worked out a plan of outpatient group therapy that in general has had good results as measured by effective living and functioning in school, at home and with peers. Groups were limited to eight patients and meetings were held once a week with two co-therapists of different sexes. Therapists usually did not try to turn discussions in one direction or another. More active than in usual group work, the therapists did not hesitate to be didactic or educational as the topic or problem indicated.*

At termination of the group sessions, usually at the end of a school year as a natural time of leave-taking, the members who had benefited sufficiently faced the departure with little emotional wrench; those who had not were resentful, anxious, disappointed or relieved.

THERAPISTS IN THE psychiatric outpatient service at Los Angeles County General Hospital have evolved a plan of group therapy for adolescent patients that has brought good results.

The Los Angeles County General Hospital, one of the largest hospitals in the world, has a psychiatric unit in which there is an inpatient children's service and an inpatient adolescents' service. There is an active, large psychiatric outpatient unit for children and adolescents. All the children's psychiatric services are integrated into one unified service, permitting an extraordinary flexibility of service and training.

The hospital is located in East Los Angeles, a marginal area with a population of Mexican origin, Negroes and lower class Caucasians. Many families are on public assistance. Broken homes, parental desertions and multiple marriages are frequent. Clinic experiences for many of these families have not been pleasant or rewarding for them. It is only in recent years with the impact of many agencies working in such areas that families seek psychiatric help without the pressure of the school or the Bureau of Public Assistance.

The author's special interest in adolescents was well known in the community; and this, in addition to a newly opened Adolescent Ward, led to increased referrals to the clinic. Our interest was evident in the processing of the families and their young people. Feeling a special responsibility toward families of the kind described above, we tried to "hang on" to them in every way we could.

That the adolescent period is a fascinating one, and one that is receiving increasing attention, is readily apparent. There is no clear-cut definitive technique for treating adolescents either individually or in group therapy. The approaches vary according to many factors—milieu, administrative expectations, whether the setting is a residential or psychiatric hospital or an outpatient clinic or private practice. Such factors have a bearing on

---

From the University of Southern California School of Medicine, and the Children's and Adolescents' Psychiatric Services, Los Angeles County General Hospital, Los Angeles.

Submitted 26 November 1965.

Reprint requests to: Department of Psychiatry, USC School of Medicine, 1934 Hospital Place, Los Angeles, California 90033 (Dr. Teicher).

the goals and on the kinds of disturbances encountered. Nonetheless, all adolescents have a common bond and common problems to master even if therapists do not have a common agreed-upon technique.

All adolescents have to master reawakened oedipal fantasies; to emancipate themselves from the dependent position that is much complicated by prolonged, enforced social and economic dependency of today; to achieve a sense of identity, of "who I am," with a beginning commitment to a life style and goal which society will recognize; to achieve a heterosexual orientation; to develop standards, ethics and a morality on their own. Many forces may interfere with the achieving of the psychological maturity to cope with these tasks, yet to move across adolescence to psychological maturity requires that the job be done.

It seems that for adolescents group therapy should be a natural therapeutic approach, for aren't adolescents group minded, influenced by their peers and peer group standards? We sometimes forget that while this is so, the intrusion of an adult in a special role sets up other forces, for any adult statement is a criticism to the adolescent, particularly the younger youth whose defenses are so fluid. Slavson, in a discussion, once called this the "paranoia" of the teenager. Nonetheless, any measures that free the youth to become more effective so that healthy maturation can occur are a form of therapy.

A group therapy way of working with outpatient adolescents has evolved at the Los Angeles County General Hospital. All prospective candidates for the group are seen first by one of the group therapists. In the clinic process parents must apply; hence much data are obtained from parents and other sources, which, of course, help in evaluating the young person clinically.

Group Composition

To give an example of the group therapy method that has evolved, this paper will focus on a group of girls. The age range was about 15 to about 17 years of age although if the maturity of a youth was such that she could fit into the group, the chronological age was no barrier. Thus, in one group there was a bright, well developed girl of 13 and an 18-year-old whose maturity was considerably less. As a rule, however, an attempt was made to keep within the age range because of the more frequent common interests and inner psychological states. The size of the group was limited to eight as a workable number. No one was accepted for the group unless motivated for help; none were coerced into the group except implicitly (the group offering the only therapy available). Some needed individual help before entering the group; some of the sicker ones needed support outside the group, even brief periods in hospital.

The diagnostic categories varied from adjustment reaction to borderline psychosis, and in one instance included a hallucinating schizophrenic girl who had sufficient islands of reality. Groups were of one sex. (In mixed groups there was interference in exploring sexual material in a significant, meaningful way. Also, the mixed groups tended to be overstimulating experiences, interfering with group work. This may be true particularly of the hospital groups because of a usual history of early sexual experiences.)

The groups were perforce open-ended. Thus, young people were present for varying lengths of time and new members were added as others departed. On the average each youth spent at least a year in the group which met once weekly for an hour and a half. While it is not economical or always practical, it is best if there are two co-therapists of opposite sexes. The family, transference and identification implications are thus much enlarged. Incidentally, most of the parents of the adolescents are worked with either individually or in groups. The co-therapists met periodically with the staff working with the parents.

The Therapist

Not everyone can do group therapy, nor can everyone who does group therapy work with adolescents. The therapist working with adolescents must have a thorough knowledge of the adolescent era, of the normal adjustive devices and defenses of adolescence, of the adolescent as a person, and of group process. Unless he has a genuine respect and liking for young people, there is difficulty. Unless he is aware that parents are people too, there is difficulty. Unless he has a sense of humor and much tolerance, the role of the therapist can be onerous.

The therapist represents an adult who has many roles, and many roles are thrust upon him. He represents reality, authority, educator. And in his very person and attitudes—which are quickly "read" by the group—he represents values, ideals, standards, ethics, morals. If the population of the group is from the lower classes or lower middle classes, it is essential that he understand the special social, familial and cultural milieu of the group members which may affect the goal one has for the group or a group member.

To the therapist, all that happens in the group has meaning whether the talk is of hats or dresses or is of the so-called "idle" kind. He has to become sensitized to the youth's talk and language and listen not only to the manifest content but the underlying emotional attitudes expressed.

The male therapist should be dominant in the group. Most of the girls in the groups here discussed had no father at home or in some Negro families the mother was very strongly dominant. Girls test their femininity and acceptance of the female role on their fathers, and a dominant male figure interested in them helped with this task as well as to establish the image of the male as something other than non-existent or in the shadowy background.

Group Structure

The youths selected and willing to participate in the group already had contact with one or the other group therapist in the evaluation process. Preparation for the group took place in these initial individual sessions with the simplest explanations that essentially "we were all to work together." The meeting time was scheduled to be most convenient for all, which meant that it was really a little inconvenient for everyone and that most young people had to take off a half day from school.

Many approaches were tried to initiate the group, such as greeting each one by name, while the therapist observed how they became acquainted; or asking each one to identify herself, the therapist observing the acquaintance process. An approach found to be valuable is to point up that each one came voluntarily for help and to ask each what she hoped the group could do to help her. This often led to a facilitation of a group feeling in that their interdependence and the assistance of one to the other were usually reiterated. An introduction now being used is for the therapist to ask each one not only to identify herself but to state as well as she can and as much as she can of the problems for which she wishes help. The procedure is followed for each newcomer admitted to the group, even though it temporarily interrupts the group work. All members of the group knew that the therapists knew the presenting problem.

Once members of a group were in the meeting room they were expected to stay until the meeting was over. Not once in a number of years has a youth walked out. There are no distractions such as radios, objects of art or the like. The furniture is comfortable chairs, a table and ash trays. The attitude in the meetings is that anything can be said, rather than done, and the confidential nature of the material discussed during the sessions is stressed. It was fascinating to see how the young people did indeed keep private what was divulged—even that one of the members was pregnant.

Implicit in the group structure was the understanding that the therapists would deal with the school authorities, police, parents or employers when reality circumstances so demanded. Implicit also was the expectation that the group would set the pace and the controls for the discussions, but that if they needed direction in this discipline, the therapists would help. The effect of this structure was a feeling of safety and security, an implicit promise they would be helped, that indeed there were solutions to problems and that adolescents could be understood and could understand.

A fortunate accident was turned to therapeutic advantage. Until a new clinic building was available, the first meetings of the group were in an office of the inpatient children's service, a locked ward. The office was locked to keep the children out and insure some privacy. Probably this helped the expectation that no one would leave. After the group meeting, the members expressed a desire for something to eat or drink. All wandered into the ward kitchen and each one had chocolate milk. It became an accepted ritual at the end of each meeting to go to the kitchen for chocolate milk, regardless of how difficult the session might have been. So, no matter what was expressed in the session, the "parents" loved and fed the child the symbol of love.

Group Process

In general, the therapist in adolescent groups is more active than therapists in adult groups. Depending upon the group composition at the time and the problems with which the group is working, the therapist may well be an educator. For example, in the group of girls, questions arose about sexual differences and sex anatomy. Diagrams were used to illustrate—and educate—and from this role the therapists stepped back and sexual fantasies and anxieties came to the fore. Questions arose about contraception. Information was given. Questions about sexual relations were answered, with group discussion focusing on what it meant to the girl to have them and what it meant to her that the boy cared not at all about contraception and was perfectly willing for her to risk pregnancy.

Since there was so much work to do with adolescent patients, it did not matter where the group started—whether with personal problems or with discussions of race riots, the elections or various kinds of occupations. After all, any assistance that frees anxiety-bound energy frees energy for the task of maturing and the growth of the personality.

The question of facilitating the group process was examined. The stay in the group was usually from September to June, with a summer break; and although it was an open-ended continuous group, not often did a girl return the following September unless she had begun late in the year. The therapists felt that they had two tasks to carry out in this period of nine or ten months: (1) Helping in the group process with the presenting problems of the youths—problems which prevented them in many instances from dealing with the psychological work of adolescence; and (2) helping with the psychological work of adolescence, although in many of them this could proceed if they were freed sufficiently of pathological defenses and constricting, inhibiting anxieties.

With these tasks and the time limits in mind, the therapists worked out a general plan that has been followed with good results as measured by effective living and functioning in school, at home or with peers. It was found that by making use of the presentation of problems by the group as a starting point, the therapist could turn the discussion in such a way as to help the members with problems of dependence-independence, of sexual anxiety and orientation, of identity and goals, of sibling and parent relations, of peer relations and others. Sometimes the group readily took up such discussions. But if they backed away, as sometimes they did, the therapists could be didactic, raising questions applicable to the problems of all adolescents—not just the specific problems of group members. Usually that did not "push" the group to a discussion of the subject. Yet, in later follow-up, it was found that the young people graduating from the group remembered most how supportive and "freeing" such information had been to them. Adolescence is a unique era. The adolescent struggles with his uniqueness and gains much relief from sharing with his peers the universality of their questions, doubts, feelings and troubles. Intrusion of the therapists' discourses into the group meetings had the effect of showing the members that they did share these problems.

Termination

Since the staff had learned that the summer break was so common an ending period, plans were made for a rounding out and termination of the therapy at that time.

The approaching recess was a legitimate occasion for discussing plans for the vacation and for feelings about leaving the group and one another. Those who were ready to leave, who clinically showed improvement, felt secure enough to discuss leaving their group "siblings" and "parent" figures with confidence that the siblings and parents would not lose interest in them or cease to be available for help. The secure members could make a normal separation much as a healthy youth does when leaving home for school or camp. Others expressed anger at the recess, or relief that the sessions were ending; and some said that it was too good to be true to have any stable family, or that it was too anxiety-producing to get as friendly as they had been. Those still insecure said such things as "What's the use, nothing really lasts"; "You can't count on anyone or anything"; "People aren't interested in you really"; Doctors take vacations when they want to, no matter what the patient needs." Patients of this order frequently separated from the group prematurely—before the therapists thought they should.

When problems about termination and separation were introduced, the therapists did not hesitate to voice sentiments and feelings if the group was unable or hesitant to articulate them.

Little League Shoulder

Osteochondrosis of the Proximal Humeral Epiphysis in Boy Baseball Pitchers

JOEL E. ADAMS, M.D., *San Bernardino*

■ *Roentgenographic changes consistent with osteochondrosis of the proximal humeral epiphysis were observed in five young baseball pitchers complaining of shoulder pain in the throwing arm. The symptoms and findings were quite similar to the previously reported involvement of the medial epicondylar epiphysis or "Little Leaguer's elbow."*

The act of throwing a baseball hard is an abnormal whip-like action which places a forceful repetitious traction strain on the shoulder joint.

Shoulder pain in youngsters engaged in organized competitive swimming programs can also be explained in this way.

Since these entities became evident with the establishment of organized baseball programs for boys in this age group, better medical supervision and rule changes to limit the amount of pitching until the epiphyses close, are urgently needed.

PAIN IN THE shoulder or elbow with attritional changes involving these joints is an accepted occupational hazard among professional baseball pitchers. Since the establishment of Little League and Pony League baseball programs for boys in the nine to 15 year age group, the vulnerable ununited epiphyses of young participants have been subjected to the same unusual repetitious strain demanded of adult pitchers.

"Little Leaguer's elbow" has become a common affliction. X-ray studies of elbows of 162 youngsters (previously reported) demonstrated this to be primarily a medial epicondylar epiphysitis or osteochondrosis commonly involving traction type epiphyses such as the tibial turbercle and os calces as described by Osgood-Schlatter and Sever many years ago.

When the first young pitcher with shoulder pain came to the author's attention, an attempt to conduct a similar study of shoulders was unsuccessful, mainly because of apprehension on the part of managers, parents and youngsters that it might prevent the boys' pitching.

Although the proximal humeral epiphysis is not normally classified as a traction type, it assumes this status when one analyzes the role of the shoulder in the mechanism of the throwing act as required by a baseball pitcher. Like the handle of a whip, the shoulder acts as a stabilizing base for the forceful follow-through flail of the arm and forearm similar to a whiplash action. There are two separate sets of muscles playing a primary role in the throwing act. A heavy external group such as the pectoralis major, deltoid and triceps which attach to the humerus distal to the proximal epiphysis, and a finer internal group of ro-

---

Submitted 14 March 1966.

Reprint requests to: 1236 Waterman Avenue, San Bernardino, California 92404 (Dr. Adams).

tators—the supraspinatus, infraspinatus and subscapularis which attach to the tuberosity of the humerus proximal to the epiphysis. At the completion of the throw, there is a powerful drag or pull on the head of the humerus away from the glenoid fossa. This pulling force is transmitted through the proximal humeral epiphysis, subjecting it to an abnormally repetitious traction strain.

Pain in the shoulder which occurred only at the end of a hard throwing motion and which could not be accurately localized was the principal symptom in five boys who were examined. Results of physical examination of those patients were within normal limits except for obvious overdevelopment of the shoulder girdle muscles of the throwing arm, slight discomfort to firm digital pressure over the proximal humerus, and duplication of the pain by simulating the traction force of a hard pitch.

Comparative x-ray studies of both shoulders showed the following changes in the throwing arm: Widening of the proximal humeral epiphysis, demineralization and apparent fragmentation without evidence of avascular bone necrosis, and accelerated growth. These changes are consistent with local inflammatory reaction to repeated trauma. They are self-limiting and they subside rapidly with rest and avoidance of the aggravating trauma, which is probably the reason not many youngsters with shoulder pain seek medical attention.

Because of the absence of bone necrosis, Goff[5] has classified these transient changes as false osteochondroses as distinguished from true osteochondroses involving pressure type epiphyses such as occur in the hip in Legg Perthes syndrome, in the tarsal navicular in Kohler's disease, and in the metarsal head in Frieberg's disease.

In evaluating the findings noted in the five previously mentioned cases, it became obvious that the frequent complaint of shoulder pain among youngsters engaged in organized competitive swimming programs could also be explained on the same basis. These programs, like baseball, are sometimes over-enthusiastically conducted, requiring from one to two hours of maximum effort daily, seven days a week, over and above normal recreational swimming. The various competitive swim strokes not only put a repetitious traction strain on the proximal humeral epiphysis but also on the epiphyses of the corocoid and acromial processes of the scapula to which are attached the short head of the biceps, the coracobrachialis and the deltoid muscles.

Haas has generally been credited with having described osteochondritis of the head of the humerus in 1921, but in a thorough search of the literature no publication on the subject was found. In 1953 Dotter[4] reported a case of a 12-year-old Little League pitcher with shoulder symptoms and roentgenographic changes identical to those in the first of the five patients reported upon herein. However, because of the void in the literature on the subject and lack of a better explanation, Dotter diagnosed the lesion as a fracture through the epiphyseal cartilage.

Reports of Cases

Case 1—A 13-year-old left-handed pitcher had pitched one year of Little League and was trying out for Pony League when he began having left shoulder pain when he threw hard. After three weeks, the pain became so severe he had to stop pitching and he then sought medical advice.

On examination the shoulder joint showed a complete range of painless motion with very slight tenderness to deep pressure over the proximal humerus. The shoulder pain could be induced by jerking on the outstretched arm in a way that simulated the completion of a hard throw. The patient was reluctant to go through the throwing motion voluntarily because of anticipated pain. Comparative x-ray studies of both shoulders (Figure 1) showed demineralization and decided widening of the epiphyseal line in the pitching arm.

Treatment consisted simply of discontinuing playing for the remainder of the season. The

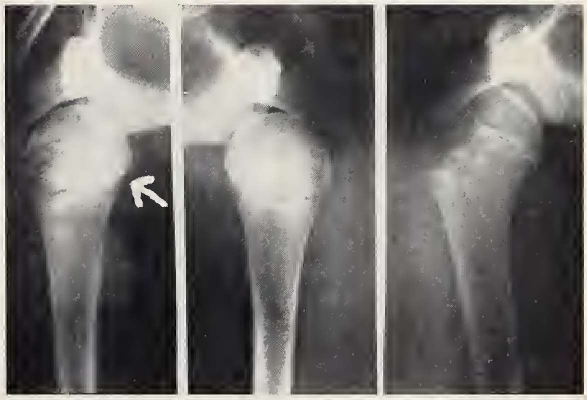


Figure 1.—(Case 1) Film at left shows decided widening and demineralization of proximal humeral epiphysis (arrow) in the left arm as compared with the right arm, shown in center frame. The right frame shows healing of the affected arm after several months' rest.

symptoms were completely relieved and the roentgenographic appearance of the proximal humeral epiphysis became essentially normal. The patient was advised not to resume pitching until the epiphyses closed but was told he might play other positions and engage in other sports.

CASE 2—A 14-year-old right-handed pitcher who had pitched since age nine and played outfield and catcher on days he was not pitching, began to have pain in the right shoulder when throwing hard. It gradually became more severe and finally he had to stop playing. He had been treated for Osgood Schlatter's disease at age 12, which indicated a pre-disposition to epiphyseal involvement. On physical examination overdevelopment of the right shoulder girdle muscles was noted and pain was evoked on simulation of a hard throwing motion.

Comparative x-ray films (Figure 2) showed widening of the epiphyseal line and fragmentation. With complete rest from throwing, the shoulder pain subsided and x-ray films several months later showed return to normal appearance of the proximal humeral epiphysis. The patient resumed playing ball but was told not to pitch until the epiphyses had closed.

CASE 3—A 15-year-old left-handed pitcher who had pitched for five years and played first base on days he was not pitching, began to have shoulder pain when he started practice at the beginning of the season. Pain was felt in both the front and back of the shoulder but only at the end of a hard throwing motion. Pain gradually became severe enough to force the patient to stop throwing and to seek medical attention. On physical examination overdevelopment of the shoulder girdle muscles of the throwing arm was noted and discomfort was evoked by firm digital pressure over the greater tuberosity of the humerus and also in the postero-inferior glenoid region. Comparative x-ray films (Figure 3) showed widening of the proximal epiphysis, deformity and demineralization of the greater tuberosity and exostosis from the postero-inferior margin of the glenoid fossa. (The latter lesion, one that is commonly found in professional pitchers, is a reaction to repeated traction stress at the attachment of the long head of the triceps and posterior capsule.) The patient was advised to rest the arm until the symptoms subsided and to play first base if he intended to continue in baseball.

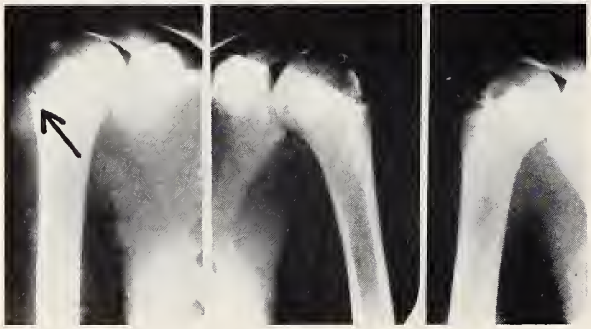


Figure 2.—(Case 2) Widening and fragmentation of the proximal humeral epiphysis (arrow) as compared with the opposite arm in center frame. Film on right shows healing after several months' rest.

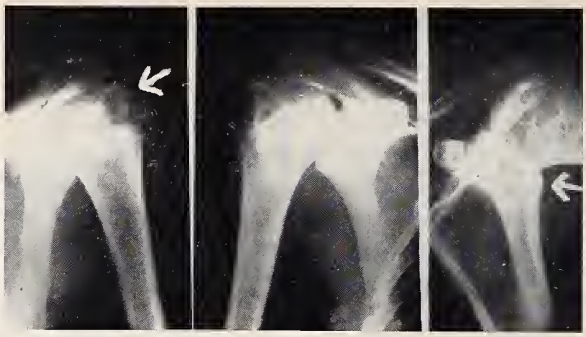


Figure 3.—(Case 3) Deformity and demineralization of the greater tuberosity of the humerus (arrow) and widening of the proximal humeral epiphysis as compared with the opposite arm (center frame). Film at right shows exostosis (arrow) from the postero-inferior margin of the glenoid fossa.

CASE 4—A 13-year-old right-handed pitcher had pitched one year in Little League, had played outfield on days not pitching and admitted considerable throwing practice at home when not playing. When he was trying out for pitcher at the beginning of the season, his shoulder began to hurt and finally became so painful that he quit pitching and stopped playing ball entirely for a time but did not seek medical attention. Three months later, he was talked into reporting for examination by one of the other patients because he was still having some discomfort when he tried to throw hard.

On physical examination the only abnormality observed was overdevelopment of the shoulder girdle muscles of the throwing arm. Comparative x-ray studies of the shoulders (several weeks after he had quit pitching) showed no significant change in the proximal humeral epiphysis. Quite striking, however, was the accelerated growth of the hu-

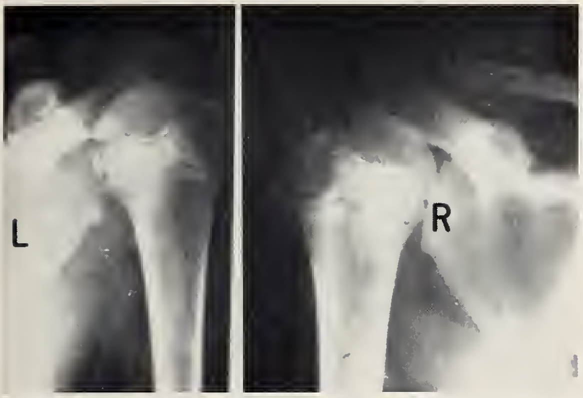


Figure 4.—(Case 4) Pronounced acceleration of growth of the right humerus as compared with opposite arm.

merus as compared with the opposite arm (Figure 4). The patient was told that he might play other positions but was advised not to resume pitching until the epiphyses had closed.

Case 5—A 15-year-old right-handed pitcher was seen several weeks after he had voluntarily stopped pitching because of shoulder pain. He had been pitching since age nine and had also experienced elbow pain in previous years.

On examination overdevelopment of the shoulder muscles of the throwing arm was noted. There was no demonstrable localized tenderness. Comparative x-ray films showed slight residual widening and demineralization of the proximal humeral epiphysis. He was advised not to pitch again until the epiphyses had closed but was told he might play other positions.

Conclusions

Roentgenographic changes and a clinical course characteristic of osteochondrosis of the proximal humeral epiphysis identify this condition as the cause of shoulder pain in boy baseball pitchers. This new entity, like the much more common "Little League elbow" involving the medial epicondylar epiphysis, has developed since the establishment of organized baseball programs in the nine to 15 year age group. Because the shoulder pain is felt only at the end of a hard throwing motion, rapid recovery results when the youngster stops pitching. As he usually stops voluntarily, medical attention is not often needed, which explains the dearth of the medical literature on the subject.

When the rules regulating the amount of throwing by pitchers in the Little and Pony Leagues were drafted, there was no definite medical knowledge available as to what effect the abnormal repetitious throwing motion that is required of pitchers would have on the ununited epiphyses of the arm. Unfortunately, despite the subsequent accumulation of medical evidence demonstrating the need for further protection of the young pitching arms, there has been a reluctance, especially on the part of Little League administrators, to alter the present rules.

After an extensive study of the so-called Little Leaguer's elbow, the following recommendations were made by the author and it appears that they bear repeating as applicable to similarly caused pain in the shoulder.

- Restrict pitchers in Little League to two innings and in Pony League to three innings per game.
- Encourage pitchers to report shoulder or elbow pain immediately and to discontinue pitching (although playing in other positions) until the epiphyses are closed.
- Advise pitchers not to practice at home before, during or after the baseball season, as excessive throwing invites trouble rather than perfection at this age.
- Abolish curve ball throwing at this age, as it not only puts additional strain on the arm but requires excessive throwing practice to perfect.
- Establish medical advisory boards at national and local levels, and persuade coaches not to try to treat or to recommend a method of treating sore pitching arms.

REFERENCES

1. Adams, J. E.: Injury to the throwing arm—A study of traumatic changes in the elbow joints of boy baseball players, Calif. Med., 102:127-132, February 1965.

2. Bateman, J. E.: Athletic injuries about the shoulder in throwing and body contact sports, Clin. Orthopedics, 23:75-83.

3. Breck, L. W.: Personal communication.

4. Dotter, W. E.: Little leaguer's shoulder—Fracture of the proximal humeral epiphyseal cartilage due to baseball pitching, Guthrie Clin. Bull., 23:68-72, July 1953.

5. Goff, C. W.: Legg-Perthes Disease and Related Osteochondroses of Youth, Charles C Thomas, 1954, Springfield, Illinois.

6. Middleman, J. C.: Shoulder and elbow lesions of baseball players, Amer. J. Surg., 102:627-632, November 1961.

7. Slocum, D. B.: Mechanics of common shoulder injuries, Amer. J. Surg., 98:395, 1959.

Planing for Precancerous Skin

A Ten-Year Evaluation

ERVIN EPSTEIN, M.D., *Oakland*

■ *A 10-year follow-up of 10 patients with precancerous cutaneous alterations that could be expected to recur (actinic keratoses, radiodermatitis, leukoplakia) revealed that dermabrasion gave excellent results in four cases and at least some benefit in four others.*

While planing is not a panacea for the premalignant skin, this study suggests that it is of prophylactic value in the control of this condition in a reasonable proportion of cases.

UNFORTUNATELY, medicine has experienced and in all probability is still experiencing, therapeutic fads that have gained widespread acceptance but which have waned with further evaluation or the development of newer and more successful approaches. Dermabrasion is an example. It was acclaimed as a cosmetic procedure for a number of years but use of it now has decreased to a comparative trickle.[2]

Planing for therapeutic usage, or more properly for its prophylactic properties, did not attain the same degree of popularity as did its use for the eradication or minimization of scarring. To date, the study performed by Burks and his coworkers in which they planed only one side of the face in patients with precancerous skin, is the only controlled study of the effectiveness of this method.[2]

This approach was first suggested in an article published in 1956 describing the benefits obtained in three patients with radiodermatitis, leukoplakia and actinic keratosis.[3] Two years later, it was evaluated further by means of a questionnaire.[4] The data presented in that article established that the short-term results in such cases were considered to be promising by a representative group of physicians. The entities investigated included actinic or senile skin, radiodermatitis, leukoplakia, xeroderma pigmentosum and epitheliomas.

Burks' report was based on a study of 15 patients followed for from 18 months to five years. As I had treated such patients in this manner since 1954, I decided to recall as many as possible of the early patients for reevaluation. Ten of the pioneer subjects were available for such consideration.

Results

Ten patients were followed for from eight to 12 years. While this is a small series, the length of observation lends value to the findings. The total patient-years was 99, the average was nine and nine-tenths years and the mean and the median were both 10 years. Therefore, one could consider this to be a 10-year study.

The results were classified as successful in four instances (no recurrences), partially successful in four cases (recurrences but definite benefit) and failure in two patients (fairly early recurrence or the development of malignant neoplasia).

From the Departments of Dermatology, University of California School of Medicine, San Francisco; and Highland-Alameda County Hospital, Oakland.

Submitted 13 April 1966.

Reprint requests to: 447 29th Street, Oakland, California 94609 (Dr. Epstein).

Actinic skin. The treatment failed in one of five patients with actinic skin. That patient, a rodeo rider with extensive keratotic, epitheliomatous and sarcomatous alterations, noted keratoses four months postoperatively. Since then he has had many keratoses and epitheliomas in the treated areas. Another man, who had recurrent keratoses and epitheliomas before dermabrasion was carried out, had considerable improvement after operation, but not complete freedom from further keratoses. The other three patients have had no further keratoses or epitheliomas although two of them continued to have keratoses in unplaned locations. One of the latter patients was an albino.

Leukoplakia. Three patients with leukoplakia of their lower lips were treated with dermabrasion. Healing was prompt in all cases. The cosmetic results were excellent. Two had recurrences—in three months in one case, in two years in the other. After removal of these lesions, neither of these patients had further trouble and so were classified as having obtained partial benefit from this procedure.

Radiodermatitis. Both subjects in this category had recurrences of keratoses after dermabrasion. One of them, who had a severe chronic x-radiation reaction on his chest, back and shoulders, did not respond at all to this treatment. The other, who had an occupationally-caused radiodermatitis of her hands, noted keratoses one year after planing. However, the treatment was successful enough that contemplated amputation could be abandoned and the result therefore was classified as partially beneficial.

There were no complications, pigmentary or otherwise, in these patients. The recurrences were in the form of keratoses or leukoplakia in all instances except one in which multiple recurrent basal-cell epitheliomas were noted during the nine years of observation. The latter patient had actinic damage to his skin.

Evaluation

From the foregoing, it is obvious that dermabrasion is not a panacea for the precancerous skin. It must be emphasized again that it is the prophylactic, not the therapeutic, values that are being assessed in this investigation. While the results were classified as failures in two cases and as only partially successful in four, it must be noted that excellent results were obtained in four of 10 patients who were followed for an adequate period. There is no other approach available at this time that can match these proportions in such cases. While one cannot guarantee a perfect result to the prospective patient, these data should be encouraging to a person who has been made a "dermatologic cripple" by recurrent epitheliomas and keratoses. This approach is considered to be a definite contribution to the management of the precancerous skin.

Originally, it was thought that the failures (recurrences) were due to further exposure to the causative agent (sunshine, x-radiation, smoking). However, in this survey it was noted that the recurrences developed promptly (usually within three months to two years). Since the patient would not be likely to encounter sufficient amounts of these carcinogens within so short a period to explain such changes, it is likely that the recurrences are due to the nature, severity and depth of the condition (chronic radiodermatitis, severe actinic keratoses and epitheliomas) or to technical factors (too shallow planing).

The planing machine should not be discarded. It is of value in the prevention of cutaneous malignant change in carcinogen-damaged skin. This is underscored by the fact that of 1,075 dermatologists replying to a questionnaire in 1961, 194 had used planing for the management of the precancerous skin and 36 (18.5 per cent reported their results as excellent and 115 (59.5 per cent) as good—a total of 78.0 per cent.[2]

REFERENCES

1. Burks, J. W., Marascalco, J., and Clark W. H., Jr.: Half-face planing of precancerous skin after five years, Arch. Dermat., 88:572, November 1963.

2. Epstein, Ervin: Present status of dermabrasion, Calif. Med., 98:79, February 1963.

3. Epstein, Ervin: Planing for precancerous skin, A.M.A. Arch. Dermat., 74:312, September 1956.

4. Epstein, Ervin: Planing for precancerous skin: A follow-up study, A.M.A. Arch. Dermat., 77:676, June 1958.

Experience With Dimethyl Sulfoxide

LEONARD MARMOR, M.D., AND BARBARA WALIKE, R.N., M.S., *Los Angeles*

■ *One hundred and thirteen patients were treated in the orthopedic clinic of the University of California, Los Angeles, with 70 per cent dimethyl sulfoxide twice daily for a period averaging 7.2 weeks. Evaluation of the results revealed little if any therapeutic effect for patients with arthritis.*

DIMETHYL SULFOXIDE (DMSO) since its public introduction in a news release from the University of Oregon in December 1963 has been the center of a great deal of publicity and numerous discussions and reports.[3] Little has been reported in medical journals, although many readers of news reports seem to have concluded that DMSO has unlimited uses. Among the many effects attributed to this relatively unknown drug are local analgesia, decreased swelling, promotion of healing and the ability to pass through the skin barrier.[2] Its suggested clinical uses have emphasized orthopedic and dermatologic problems but only a small number of cases has been reported.

This communication is a report of the use of DMSO in the therapy of 113 patients treated at the University of California, Los Angeles, since July 1964.

Dimethyl sulfoxide is a solvent that has been known for almost a hundred years and is closely related to acetone. It was first synthesized by Saytzeff in 1867 and at the present is a by-product of the wood pulp industry. DMSO is a clear, colorless fluid with a freezing point at 18.4°C, a boiling point of 190°C and a density of 1.1.

Method of Study

The patients were unselected and included all patients who had conditions that might respond to DMSO therapy. The largest group in this series were patients with rheumatoid arthritis of grades III and IV.

Dosage

Patients in this study were prescribed medical grade DMSO* 70 per cent in quantities of 4 to 16 ounces. Instructions were given as to the method, amount and frequency of application. Approximately 5 to 15 ml was applied twice a day to a broad area of the skin which included not only the area of the affected joint or condition, but a considerable surrounding area. It was to be applied with a cotton swab or brush until the area was thoroughly saturated, and then allowed to dry for 30 minutes.

The patients usually returned to the clinic in two weeks and between visits were contacted by telephone. Verbatim records were kept on each patient's statements about the drug.

The evaluation form provided for the rating of symptoms on the following scale: 3, severe; 2, moderate; 1, slight; 0, none. On the basis of these records, patients were then classified according to their response to DMSO. The following criteria of response were used in evaluation of the result:

None—No positive response or negative response.

Fair—Some temporary improvement in symptoms for periods up to six hours. This included patients reporting "slight improvement in pain."

From the University of California, Los Angeles, School of Medicine, Department of Surgery/Orthopedics, Los Angeles.

Submitted 3 December 1965.

Reprint requests to: Department of Surgery/Orthopedics, University of California, Los Angeles, School of Medicine, Los Angeles, California 90024 (Dr. Marmor).

*Supplied by Merck, Sharp & Dohme, West Point, Pa.

TABLE 1.—*Results of* DMSO *Therapy in 53 Patients with Rheumatoid Arthritis*

Diagnosis	Number of Cases	Improvement				Average Duration of Therapy (Weeks)
		None	Fair	Good	Excellent	
Rheumatoid Arthritis	53	33	12	8	–	8.0
Osteoarthritis						
Hand	9	7	1	1	–	
Knee	7	7	–	–	–	
Hip	1	–	–	1	–	
Cervical	5	4	–	–	1	
Totals	22	18	1	2	1	5.3

Good—Pronounced improvement in symptoms for periods up to 12 hours, including definite relief of pain.

Excellent—Complete relief of symptoms on a twice daily application, or permanent relief.

In applying these standards, if there was a doubtful or equivocal report the patient was assigned to the lower of two possible ratings.

The average follow-up period (with DMSO therapy continuing) was 7.2 weeks and the range was from one day to 36 weeks. The duration of therapy was determined by the presence of severe side effects, the resolution of the condition, or failure over an extended period.

Results

Fifty-three patients with rheumatoid arthritis were treated (Table 1). There were no excellent results, 8 cases in which the result was rated as good, 12 in which it was fair, and 33 in which there was no improvement—failure in 63 per cent of cases. Of the patients with osteoarthritis, 82 per cent showed no improvement with the regular use of DMSO.

Patients with bursitis and associated diseases (Table 2) experienced no permanent cure of the condition. Relief, if obtained, was usually temporary. The patients with epicondylitis appeared to respond best; however, the number with this diagnosis was small.

Patients with a variety of other other problems showed very limited improvement (Table 3).

In summary, 65 per cent of 113 patients showed no improvement in symptoms during DMSO therapy. There were no permanent cures reported with the drug, and relief of pain, when achieved, usually lasted only a few hours.

Complications

The great majority of patients reported some side effects, most of which were localized to the area of skin application (Tables 4 and 5). Ten patients had to discontinue treatment because of severe side effects including severe burning, raw blisters and, in one case, blurred vision.

TABLE 2.—*Results of* DMSO *Therapy in 22 Patients with Bursitis and Associated Diseases*

Diagnosis	Number of Cases	Improvement				Average Duration of Therapy (Weeks)
		None	Fair	Good	Excellent	
Bursitis	11	7	2	1	1	6.3
Tenosynovitis	5	4	1	–	–	3.0
Epicondylitis	4	1	2	1	–	12.5
Myositis	2	1	1	–	–	12.0
Totals	22	13	6	2	1	7.2

TABLE 3.—*Results of* DMSO *Therapy in Miscellaneous Conditions*

Diagnosis	Number of Cases	Improvement				Average Duration of Therapy (Weeks)
		None	Fair	Good	Excellent	
Dupuytrens	3	2	1	–	–	7.3
Trauma	4	1	2	1	–	5.5
Low Back Pain (postoperative)	5	4	–	–	1	5.6
Scleroderma	1	–	–	1	–	6.0
Cyst-Lateral Meniscus	1	–	–	1	–	1.0
Diabetic Gangrene	2	2	–	–	–	3.0
Totals	16	9	3	3	1	5.3

TABLE 4.—*Incidence of Side Effects of* DMSO *Therapy in 113 Patients*

	Number of Cases
Number of patients reporting no side effects	17
Number of patients reporting systemic side effects	23
Number of patients reporting only systemic side effects	1
Number of patients reporting local side effects	72

The most frequent systemic effect was breath odor. Nausea, lethargy, dizziness, abdominal discomfort and numbness were also reported.

Discussion

The experience with DMSO therapy herein reported does not seem to bear out the tremendous publicity given this drug. Fewer than 40 per cent of patients with rheumatoid arthritis in the present series had a good or fair result despite the fact that many may have been prejudiced toward the drug by the publicity in lay publications. (It is well known that 30 per cent or more patients will experience a placebo effect from any medication given with therapeutic intent.) Considering the low rate of positive response, the probability of placebo effects and the heightened expectations of the patients, it is not possible to be enthusiastic about the efficacy of DMSO in arthritis. It was also apparent in the present study that if a response to the drug did not occur within the first week, prolonged therapy did not produce a change or improvement in response. This seems somewhat contrary to the findings of Rosenbaum and associates[4,5] with regard to arthritic patients. John[2] also reported that in patients with rheumatoid arthritis the effects are not very satisfactory especially if the patients have polyarthritis. Bottomly and associates[1] were not enthusiastic about the use of DMSO in rheumatoid arthritis.

TABLE 5.—*Incidence of Local Effects of* DMSO *Therapy in 113 Cases*

	Number of Cases
Itching	34
Burning	29
Drying	26
Scaling (peeling)	22
Rash	22
Inflammation	6
Blisters	6
Pain	2
Swelling	2
Decreased effusion	2

It is possible that DMSO will have a role in medicine but at present it does not appear to have much value in the treatment of arthritis or other musculoskeletal diseases.

REFERENCES

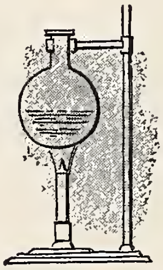
1. Bottomly, D. R., Shimazaki, Y., and Bachman, D. M.: Controlled study of dimethyl sulfoxide effects in patients with connective tissue diseases, Arch. & Rheum., 7:294, 1964.

2. John, H.: Erfahrunger mit der Therapeutischen Aneundung von Dimethylsulfoxyd in der Orthopadie (Unpublished manuscript).

3. Rosenbaum, E. E., and Jacob, S. W.: Dimethyl sulfoxide (DMSO) in acute musculoskeletal injuries and inflammations: I. Dimethyl sulfoxide in acute subdeltoid bursitis, Northwest Med., 63:167-168, 1964.

4. Rosenbaum, E. E., and Jacob, S. W.: Dimethyl sulfoxide (DMSO) in musculoskeletal injuries and inflammations: II. Dimethyl sulfoxide in rheumatoid arthritis, degenerative arthritis, and gouty arthritis, Northwest Med., 63:227-229, 1964.

5. Rosenbaum, E. E., Herschler, R. J., and Jacob, S. W.: Dimethyl sulfoxide in musculoskeletal disorders, J.A.M.A., 192:309-313, 1965.



The Chronically Draining Ear

Notes on Management in the Office

JAMES L. SHEEHY, M.D., *Los Angeles*

■ *There are three factors responsible for persistence of discharge from a chronically draining ear: Moisture, opportunistic bacteria, and debris and diseased tissue.*

In most cases, the discharge may be temporarily controlled or eliminated by office treatment:

- *Instruction of the patient in aural hygiene and impressing upon him the importance of avoiding getting water in the ear.*
- *Thorough cleaning of the ear, by the physician initially, and by the patient as frequently as necessary to keep the ear free of discharge.*
- *Antibiotics, used locally rather than systemically, and usually in the form of a powder applied by the patient daily at home.*
- *Culture and sensitivity tests when the problem does not respond to routine office treatment as outlined.*

WHAT IS THE best local medication to use for a chronic ear infection? Should systemic antibiotics be prescribed? Is a culture indicated? Are there any danger signs that dictate immediate referral to an otologist?

These are questions which we are asked frequently by physicians who are responsible for the overall care of a patient. The purpose of this paper is to answer these questions by clarifying what can be done and what cannot be done in the office for patients with chronic drainage of secretion from the ear.

Causes of Chronic Ear Discharge

There are obviously many factors which play a part in chronic ear infection. The major factors, however, responsible for the recurrence or persistence of chronic ear discharge are three: (1) Moisture, (2) opportunistic bacteria and (3) debris and diseased tissue.

Office management of the chronically draining ear must be directed at eliminating these three factors. Attention to aural hygiene and local medication will result in a dry ear in most cases.

Aural Hygiene

The patient with a perforated tympanic membrane must be thoroughly indoctrinated in the proper care of his ear. He must be advised not to blow his nose, especially during an upper respira-

---

From the Otologic Medical Group and from the University of Southern California School of Medicine.

Presented before the Section on Otolaryngology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Sponsored by the Los Angeles Foundation of Otology.

Reprint requests to: 2122 West Third Street, Los Angeles, California 90057 (Dr. Sheehy).

tory tract infection. Nasal secretion should be drawn into the throat and then spit out. This avoids the blowing of infection into the eustachian tube and middle ear.

Particular care must be taken to avoid the introduction of soap or water into the ear canal. Before washing the hair or showering, a piece of cotton or lamb's wool should be placed in the canal and covered with petrolatum. Swimming is allowed only if cotton and petrolatum are used and held in place by a tight-fitting swimming cap.

Should ear discharge occur, the patient should clean the canal thoroughly and deeply with a cotton applicator as often as is necessary to keep the ear dry. If cotton is used to keep the discharge from draining externally, it is placed in the base of the cavum conchae in such a manner that air can enter the ear canal at all times.

Aural hygiene does not stop with the patient, however. The physician must understand the importance of thorough cleaning of the ear canal to remove all pus and debris. This is accomplished either by using a small suction tube (Figure 1) under direct observation with an otoscope, or by dry wipes with cotton-wound applicators. Rarely should the ear be irrigated.

Local Medication

Often to the surprise of both physician and patient, the ear discharge may show a dramatic improvement with no other treatment than that mentioned above. In most cases, however, it is prudent to prescribe local medication.

Many bactericidal ear drops are available, the majority of them combined with a steroid. These medications are very effective in reducing the amount of discharge and in controlling any odor. For the patient with only an occasional brief flare-up of discharge with an upper respiratory infection, the use of a few drops three times a day after thorough cleaning of the ear will usually be all that is necessary.

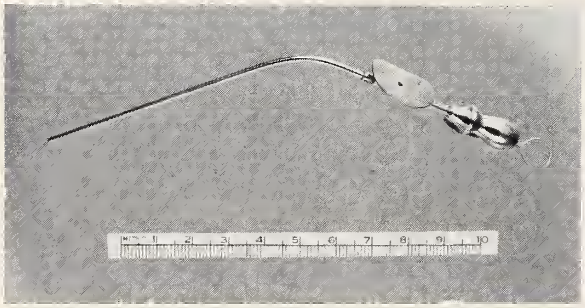


Figure 1.—Baron suction tube (No. 5) with thumb cut off. Available through V. Mueller and Storz Instrument Companies.

For the patient with a longstanding or frequently recurring ear discharge, particularly if it is malodorous, and for those that do not respond rapidly to ear drops, we have found that a dry (powder) treatment is much more effective.[3] This eliminates the apparent contradiction of trying to dry the ear by using drops, and helps emphasize to the patient the importance of keeping the ear dry at all times.

The dry treatment utilizes a broad spectrum antibiotic preparation which the patient may insufflate at home after cleaning the ear. We use a powder consisting of chloramphenicol, 50 mg, sulfanilamide, 50 mg, and amphotericin B (Fungizone®) 5 mg packaged in a No. 4 gelatin capsule. The larger cup of the capsule, containing all the powder, is placed in an Armour Inhalator (Figure 2) with the open end *facing* the bulb. (This position is contrary to the directions contained in the package, which state that the open end should be away from the bulb. However if the capsule is placed in that way, too much powder will enter the ear.)

The patient is given a prescription for three capsules. Each capsule should last for approximately eight to 10 applications of powder. He is instructed to clean his ear thoroughly with a cotton

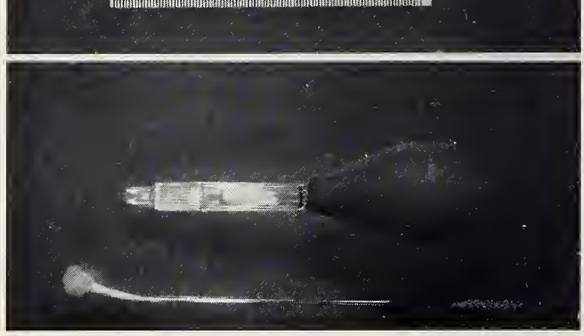


Figure 2.—*Above*, Armour Inhalator disassembled with antibiotic capsule, cotton and wire applicator. *Below*, inhalator and applicator ready for use. The *opened end* of the capsule points *toward the bulb.*

applicator until dry, then blow one puff of powder. This is repeated twice daily until the ear is dry, at which point he should clean the ear once daily and use the powder again should discharge recur.

Systemic Medication

Systemic medication may be prescribed for treatment of a respiratory infection, but not primarily for treatment of the ear. With few exceptions there are no indications for systemic administration of antibiotics to control chronic ear infection. The ear problem is caused by opportunistic bacteria which should respond to aural hygiene and local medication. More often than not the bacteria present would be found to be resistant to the antibiotics usually prescribed for systemic use.

A Culture of the Discharge?

Generally speaking, chronic ear discharge will be controlled by the measures outlined above. A culture may be taken initially, however, when one suspects that a virulent organism is present or when it appears that surgical operation on the ear will be necessary in the very near future.

If a culture is to be made, it is important to know the results within 24 hours so that appropriate therapy may be instituted quickly. For this purpose we have used the Medikit®* which provides culture plates on which specimens of discharged material can be placed immediately and incubated at room temperature in the office.[1] Results, showing the sensitivity of organisms, can be determined in 24 hours. Not only do we have the information quickly, but the patient is saved considerable expense.

Surgical Treatment?

Many advances have been made during the last decade in the surgical treatment of chronic otitis media. Elimination of infection, grafting of tympanic membranes and improvement in hearing have been made possible by combined use of operation under the operating microscope and antibiotics.[2] Although surgical treatment is desirable in all cases of chronic otitis media, the fact remains that it is not always imperative. There are, however, some guidelines that should be laid down for determining whether or not to operate:

- The ear with a central perforation from which mucoid material drains only occasionally, that responds quickly to appropriate local therapy and that has no odor is usually a "safe ear." Surgical treatment in cases of this type is elective. In contrast to this, if there is a marginal or attic perforation (Figure 3) or persistent discharge, there is potential danger and the patient should be seen by an otologist.

- There are certain "danger signs" that should be watched for, regardless of the appearance of the ear or history of discharge. Whenever any of these symptoms are present, the possibility of surgical intervention must be considered and an otologist should be consulted immediately. These danger signs are:

Ear Pain—characteristically not severe, but dull, nagging and often worse at night. This may indicate meningeal irritation.

Headache—associated with persistent chronic ear discharge or with the sudden cessation of chronic ear discharge.

Dizziness—this is almost always a symptom of urgency in patients with chronic otitis media.

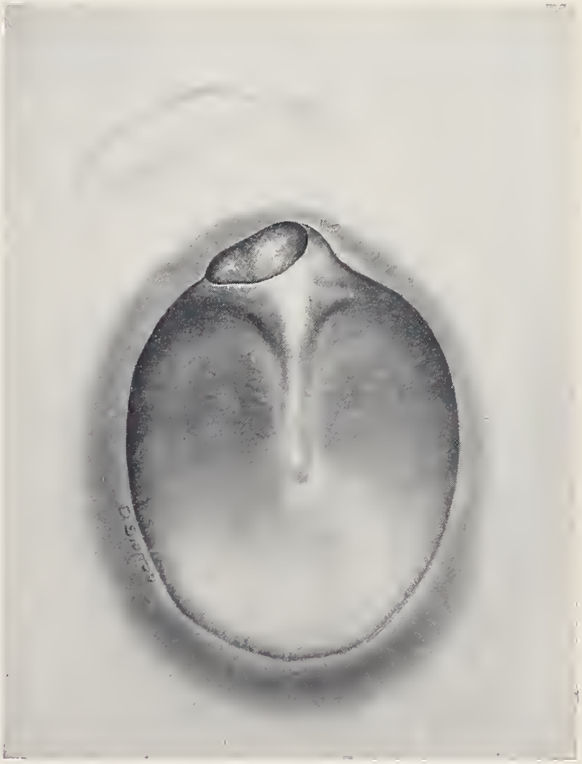


Figure 3.—Attic perforation with formation of cholesteatoma.

---

*Available from Media, Inc., 89 Lincoln Park, Newark 2, N. J.

Facial Nerve Weakness—this is due to erosion of the infection into the facial canal.

Conclusion

There is much that can be done by the family physician in caring for the patient with chronic otitis media.

Proper attention to aural hygiene and local medication will frequently result in a dry ear, thus ridding the patient of an annoying symptom and better preparing him for any reconstructive surgical procedure that may be needed.

Generic and Trade Name of Drug

Amphotericin B—*Fungizone*.

REFERENCES

1. Littman, M. L.: The office selection of antibacterial therapy, G.P., 19:125-130, 1959.
2. Sheehy, J. L.: Surgery of Chronic Otitis Media, in Otolaryngology, Hagerstown, Maryland, W. F. Prior Co., Inc., 1965, vol. I, chapter 10B.
3. Sheehy, J. L., and House, H. P.: Dry treatment of infected mastoid cavities, A.M.A. Arch. Otolaryng., 70: 509-510, 1959.

The Medical Student

NEWLIN HASTINGS, M.D., *Los Angeles*

ONE OF THE privileges a chairman has is to present an address with free license of subject. I promptly sought a subject which would not suffer in comparison with the scientific presentations on the same program. My choice is one not with academic excitement and not precise, but nonetheless of the greatest importance—The Medical Student.

This student possesses great potential for service to others and for personal rewards if his horizon can be wide enough and his vision and education are adequate. I am concerned today with three stages of his training which can be enriched by all of us: When he is a student selecting his future occupation, when he is a student in medical school considering the practice of medicine, and when he has finished his formal training.

First we should encourage appropriate students to join us in our profession, which we know is exciting and rewarding. The future need for more physicians is well recognized; yet only one-third of the college students who choose a "pre-medical" major ever apply to a medical school. Investigation has shown that often there is no active physician participation in the counseling services of many colleges in California. "Pre-med" clubs have been formed in some colleges, but several of these are relatively inactive and without participation of physicians who could stimulate interest and discuss students' questions. Three films entitled "The Making of a Doctor" have been made available by the American Medical Association and are used by pre-med clubs in a few colleges. Without help from clinicians sometimes interpretations have been left only to the senior medical student who is interested in his previous schoolmates.

Practicing physicians should offer to help college students who are considering medicine as their future occupation. Help can also be given to high school and college students by providing conferences and tours of medical centers such as now are offered by the schools of medicine at Stanford and the University of California at Los Angeles. Also at Stanford there is a program called "Day with a Doctor" which enables a student to spend one day a year with a physician in private practice. However, although these stimuli are steps in the right direction, they need expansion, not only within the universities having medical schools, but especially in colleges that do not have easy academic and geographical relationships with a medical school. Clinicians can and should be of greater service to their communities and to eager college students by offering their enthusiastic counsel.

Moreover, the student who is in the midst of his medical school curriculum needs adequate exposure to the private practice of medicine if he is to evaluate this aspect of the profession, even though he may later choose an institutional or purely scientific career. In recognition of this need, 36 of 88 medical schools in the United States have instituted preceptorships, often in the summer. Only four schools offer preceptorships with specialists. In 10 schools, the program is mandatory, while in 26 it is elective. Competing with the elective programs are other summer occupations which, significantly, bring an average summer income of $1,000. Last summer, to meet this competition at the University of Southern California School of Medicine, a charitable fund for medical projects, called Salerni Collegium (with equal help of the Los Angeles County Medical Association) sponsored a program for 11 students. Each student was assigned to a specialist and received a stipend of $100 a week.

Other preceptorships have been provided by the California Academy of General Practice. In this plan, the student does not receive any pay but has the opportunity of living with the physician in the summer. To date this program has involved 364 students, 51 from Stanford, 36 from the University of Southern California, 35

Chairman's Address presented before the Section on General Surgery at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 1136 West Sixth Street, Los Angeles, California 90017 (Dr. Hastings).

from the University of California at Los Angeles, 15 from the University of California College of Medicine, four from out-of-state schools, and the remaining 223 from the University of California at Berkeley. Obviously the participation has been inadequate, and even at the University of California, where enthusiasm was high, the plan is now inactive because of the lack of volunteering physicians. But some such program should be actively promoted, for a medical school student should have the benefit of evaluating the private practice of medicine in the community. Thereby he can obtain a broader vision, deepen his experience, have a taste of the thrill of applying scientific data to patient care and know a physician's life. Also from discussions around the luncheon tables, he can gain some insight into the present and potential impacts which socializing and economic factors will have on the future of his profession.

The third stage of the medical student with which I am concerned today is his postgraduate life. It is the one most in need of our attention. In this period, the physician must have scientific stimulation if he is to taste the satisfactions and achievements possible in the rest of his professional life. The transition from student in confined academic training to a physician practicing in a community involves changes in intellectual opportunities, in independent responsibilities, in financial demands and compensations and in status in his community of professional and lay people. Too often this metamorphosis may be associated with an altered outlook toward medicine and a decreasing zest for continuing education. The thirst for clinical experience can be met at the bedside, and the new physician may feel that this fulfills his need. At first the application of stored information of biochemical and pathologic changes facilitates his clinical learning and brings satisfaction. However, the increasing wealth of new information, with medical literature doubling every 10 years, is difficult to survey and to assess; furthermore, economic, domestic and other social factors place increasing demands on a physician's time. He may neglect continual addition of new information to his armentarium. He may begin to reject "ivory tower" data and new practices and even new ideas, placing his reliance on past knowledge and experiences. New information to supplement or alter his knowledge is essential, not only for the good of the patient (who now knows and demands more than in years past) but also for the continued vitality of the physician.

Reflection of the past brings realization that originally medical education was incidental to medical care. The relationship reversed somewhat in the 19th century, but there still was a great separation between knowledge known and knowledge taught. Fifty years ago, consequent to the Flexner report, the gap began to narrow. Now a widening of the rift has begun to develop again, this time not between what is known and what is taught in medical school, but between that acquired during formal training and that actually used for the effective art of healing in the community.

Potential teachers are being produced. There are 6,800 students enrolled in graduate and postgraduate programs, and 46 per cent of them are seeking advanced degrees in the basic medical sciences. This force is needed for research and for teaching positions. Of the budgeted positions in the 88 medical schools, 15,514 are filled and 955 unfilled. It is to be hoped the need will be met not only for teachers of medical school students, but also for physicians in practice.

Of the 13,381 interns and 40,451 residents in training, about one-third are in medical school facilities and have good educational programs. The medical education of those who are in the hospitals without medical school affiliation sometimes is inadequate. The opportunities particularly in these hospitals are not adequately used even though clinical material is usually abundant and teachers are generally present in the environs. Certainly the student fresh from the teaching institution and just entering practice could be of service to his older colleagues and at the same time could maintain habits for his own never-ending professional scholarship. In such settings, older men must encourage their new rivals.

Many teaching clinics should be developed for the good of all physicians and for the benefit of the patient community. Participation in a clinic should be not only for the ones with full staff privileges in the hospital holding the clinic but also for physicians not on the staff. A plan to offer this opportunity is now being organized at the Los Angeles County General Hospital by the University of Southern California School of Medicine. Outside physicians will be encouraged to attend outpatient clinics held every morning with all appropriate specialists attending to provide teaching based on actual patient problems as well as to facilitate prompt treatment. I hope many more hospitals will develop such plans for the dissemination of knowledge.

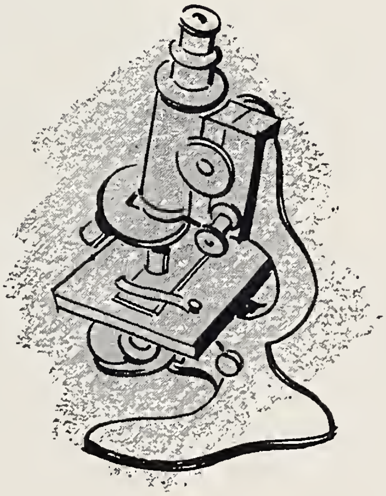
Surveys have shown that physicians in practice obtain most of their information from publications, including (and woefully sometimes too much) from the literature of pharmaceutical companies. The last National Council on Medical Education stated that a "university without walls" must be developed for the use and coordination of all methods of continuous medical education. The development of closed television programs is an addition that has great potential. In California, under the administration of Dr. Brayton at the Office of Continuing Education in Medicine and Health Sciences of the University of California Extension, Los Angeles, 70 hospitals are participating in a weekly one-hour program with five institutional producers: University of California at Los Angeles, University of Southern California, Loma Linda University, University of California College of Medicine and City of Hope Medical Center. There will be more such programs in the future, perhaps some in the evenings. Suggested as a possibility is a service through which a surgeon could, by dialing a number, be shown on a closed television circuit a film of an operative technique he is about to use.

Surveys also have shown that the second and much less often used means of education is postgraduate courses. The number of such courses is increasing, and 1,641 were provided last year (1965) in California by medical schools and some teaching hospitals. It is particularly encouraging to know that the teaching hospital participation in courses of this kind has increased in the last five years from 9 per cent to 21 per cent.

The third means of postgraduate education is through informal contact among physicians, a valuable factor well appreciated every day by all of us.

Participation in meetings is a further means of keeping informed. Presentations of topics, panel discussions and monthly reviews of hospital material can be most helpful. Also the meetings held by national, state and local associations and by special societies add greatly to the medical students' development and stimulation.

We in this Surgical Section of the Annual Session of the California Medical Association could assure the continued excellence of the programs such as the one just presented; and with combined effort we could cause a manifold increase in the number of physicians who would benefit through attendance. I hope the members of our section will promote a much greater service to medicine through education of the student in college and in medical school, and of the physician in later professional life.



CASE REPORTS

Differentiation of Dysfunction From Rupture of Papillary Muscle

ROBERT SUDRANN, M.D.
HENRY TESLUK, M.D., *Sacramento*

IN THE PAST FEW YEARS several reports have drawn attention to a rare entity usually encountered as a result of acute myocardial infarction.[2,3,4,5,9] Ruptured papillary muscle and papillary muscle dysfunction are two aspects of the same pathological process. Most cases have been discovered at autopsy but recent work by Phillips and coworkers[7,8] has established the electrocardiographic changes and the clinical findings to be expected in such cases. Because operation has been advocated for rupture and discouraged for dysfunction,[1,4] it is important to be able to distinguish between the two forms. This may be impossible to do at the present time in individual situations. The following report illustrates some of the difficulties that may be encountered in the future.

Report of a Case

The patient was a 67-year-old white woman with complaint of pain across the anterior chest of one week's duration, with no radiation to the back or arms. The pain was sudden in onset and relieved by rest but recurred at intervals. The night before admission to hospital, acute onset of chest pain again occurred and it was associated with vomiting and some shortness of breath. The pain increased in intensity during the night and persisted the day of admission to hospital, which was on 12 January 1966.

The patient's previous medical history was unremarkable. There was no history indicative of heart disease in the past.

On admission the patient was sweating and obviously short of breath. She appeared acutely ill. Blood pressure was 100/70 mm of mercury and the pulse was 80 and regular. Respirations were 25 per minute. Neck veins were moderately distended. Coarse inspiratory and expiratory rales and rhonchi were present throughout both lung fields. On examination of the heart a coarse Grade III (of VI) systolic murmur was heard over the entire precordium. There was no further description of the murmur at that time. The liver was two finger-breadths below the costal margin. Peripheral edema was not present.

It was believed the patient had acute myocardial infarction with resultant pulmonary edema. The systolic murmur was thought to be due to left ventricular dilatation as there was no previous history of heart disease or rheumatic fever. The usual measures such as administration of digitalis, morphine, aminophylline, diuretics and oxygen were carried out.

Because of a temperature elevation to 39.1°C (102.4°F) followed by a fluctuating temperature from 37.2°C to 38.3°C (99°F to 100°F), blood specimens were taken for culture. Subacute bacterial endocarditis was considered a possibility but the cultures later were reported as negative.

The patient responded to the therapy and the next day the lung fields were clear to auscultation. However, it was noted that the systolic murmur was louder. It was Grade IV in intensity, definitely pansystolic in character, decrescendo and beginning immediately after the first sound. The first

---

From the Departments of Medicine and Pathology, Sacramento County Hospital, Sacramento.

Submitted 4 March 1966.

Reprint requests to: Department of Medicine, Sacramento County Hospital, 2315 Stockton Boulevard, Sacramento, California 95817 (Dr. Sudrann).

sound was diminished. Although the murmur was heard all over the precordium, it was most intense at the apex. Thereafter the murmur did not change further.

At least two further bouts of pulmonary edema and chest pain occurred that day. Because of the murmur, chest pain and repeated episodes of pulmonary edema (and in spite of electrocardiographic findings, to be discussed later), a diagnosis of ruptured papillary muscle was made on the third hospital day. Periods of shortness of breath with bubbling rales continued intermittently. At one time it was necessary to withdraw 500 ml of blood, following which some relief was obtained. The leukocyte count stayed between 25,000 and 30,000 per cu mm. The initial blood urea nitrogen was 34 mg per 100 ml. There was a trace of sugar and a faint trace of acetone in the urine. The fasting blood sugar was 192 mg per 100 ml and fluctuated between 154 and 184 mg thereafter. Sodium, potassium, chloride and carbon dioxide were within normal range and remained so except for a slight drop in the chlorides to 92 mEq per liter. The blood urea nitrogen gradually climbed to 71 mg per 100 ml but the output of urine remained adequate and blood pressure was normal until the last day.

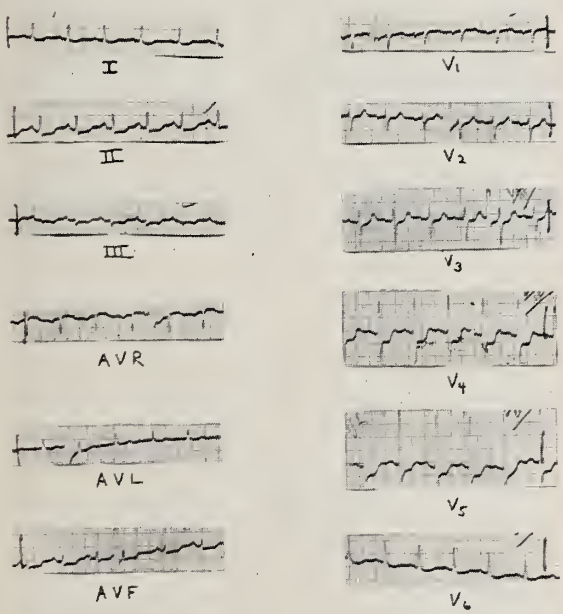


Figure 1.—Electrocardiogram on admission, showing ST-T findings compatible with Type III anterolateral papillary muscle dysfunction. See text for details.

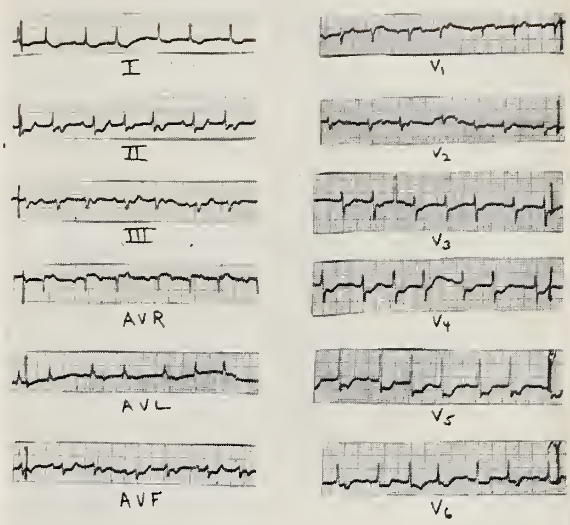


Figure 2.—Electrocardiogram three hours before death on the sixth hospital day showing second degree AV block of the Wenckebach type, as well as convex upward deformity of the ST-T interval.

Glutamic oxaloacetic transaminase (SGOT) was 39 units and lactic dehydrogenase (LDH) 730 units the day after admission. These values rose to 62 and 910 respectively the next day. X-ray films of the chest, taken with portable equipment, showed pronounced vascular engorgement. The heart appeared to be generally enlarged.

The electrocardiogram on admission (Figure 1) fitted into Phillips'[7] classification of anterolateral papillary muscle dysfunction as Type III. There was pronounced depression of the ST-T junction and a concave upward deformity of the ST-T interval. These were most pronounced in the left precordial leads but were also apparent in the other leads. No Q waves were present. An electrocardiogram three hours before death (Figure 2) showed a second degree AV block of the Wenckebach type (which had been present for two days) and a convex upward deformity of the ST-T interval along with the ST-T junction depression.

The patient's condition deteriorated steadily and on the sixth hospital day she died of intractable pulmonary edema.

At autopsy the heart weighed 450 gm. On examination of the myocardium, a gray soft area of the left ventricular wall was noted, beginning at a point near the apex and extending almost up to the base of the heart and including the anterolateral papillary muscle. This muscle itself was still intact although there was an ecchymotic granularity of the area at the junction of the muscle and the adjacent myocardium. The chordae tendineae were still attached to the papillary muscle and none showed actual destruction. After fixation, examination of a longitudinal section of the left anterior papillary muscle showed it to be extremely pale and almost totally involved by the process of infarction (Figure 3). The mitral valve leaflets themselves were essentially normal and the circumference of the valve was also within normal limits. The other major valves of the heart were also essentially normal. The coronary vessels were calcified and showed fairly severe narrowing of the lumina but no actual occlusion. In addition to these findings the lungs were greatly increased in weight due to extensive pulmonary edema and bronchopneumonia. Except for fairly severe arteriosclerosis of the aorta, there were no other very unusual features noted on the examination of other viscera. These findings were confirmed by microscopic studies. The necrosis of the papillary muscle was relatively fresh and there was a sharp reactive zone around the lower border.

Comment

Recently, attempts have been made to determine more accurately the cause or causes of a sudden appearance of a systolic murmur occurring after myocardial infarction.[4] There are four basic conditions that must be considered: Rupture of a papillary muscle; papillary muscle dysfunction; rupture of the interventricular septum; and left ventricular dilatation. Guidelines have been laid down for the differential diagnosis of each condition but much overlapping occurs and at times it is difficult to distinguish between the various entities. Because of the possibility of surgical repair of some of these conditions if the patient can survive the initial insult,[1,4,6] it is important to use all available means, including cardiac catheterization, to reach a final decision as to the cause of the murmur.

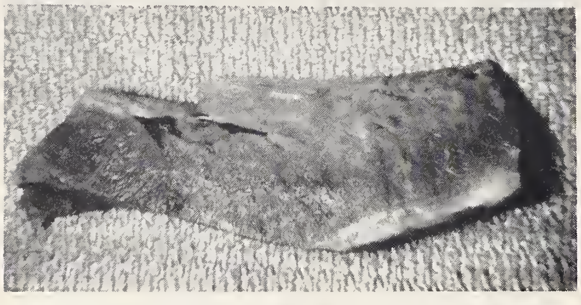


Figure 3.—Longitudinal section of the left anterolateral papillary muscle and adjacent ventricular wall, showing almost complete involvement of the muscle in the infarction process.

The case herein reported indicates some of the difficulties encountered. The electrocardiographic features were typical of those described by Phillips[7] as due to anterolateral papillary muscle dysfunction but the physical findings and clinical course suggested that rupture of a papillary muscle had occurred.[8] In their original communication Phillips and coworkers stressed the fact that the electrocardiographic changes were not specific. Some of the other conditions listed by these authors that could bring about the same changes included left ventricular hypertrophy, shock, subendocardial infarction, digitalis effects, coronary insufficiency and electrolyte imbalance. One cannot tell whether the second degree AV block that developed during the patient's illness was owing to digitalis or secondary to the severe pathological process going on in the heart. Also the ST-T wave changes were certainly compatible with several of the conditions listed above.

It is obvious therefore that the physical findings and clinical course must be considered together. In the case presented, the increase in intensity of the systolic murmur, the fact that the murmur was pansystolic and decrescendo with no gap between the first sound and the murmur, the repeated bouts of pulmonary edema and the rapidly fatal outcome all pointed to rupture of the papillary muscle, rather than papillary muscle dysfunction alone.[8] It was also shown that there did not appear to be any left ventricular dilatation so that this could not be considered as a possible mechanism for the systolic murmur. The interventricular septum was not perforated and the chordae tendineae were normal in appearance, as were the mitral leaflets. No phonocardiographic documentation of the murmur is available in this case but the heart was listened to carefully many times by several observers and there was general agreement as to what was heard. There was never felt to be a delayed onset of the murmur.

This case again indicates that there are enough clinical and electrocardiographic clues to enable one to suspect necrosis of the papillary muscle. However, differentiation of papillary muscle dysfunction from rupture of the papillary muscle may be difficult and at times impossible. Sudden appearance of a systolic murmur after a myocardial infarction, with the murmur being relatively late in systole and diamond-shaped, electrocardiographic changes as outlined by Phillips, little evidence of pulmonary edema and a generally more benign course suggest anterolateral papillary muscle dysfunction. On the other hand, electrocardiographic changes consistent with inferior wall infarction, sudden development of a pansystolic murmur, repeated bouts of pulmonary edema and early death would indicate rupture of a posteromedial papillary muscle. Should a patient of this second type survive for several weeks, prosthetic valve replacement might be feasible. In the case reported here, elements in favor of both diagnoses were present. A "gray" area between the two forms will continue to exist until more data are available and studied. Caution is suggested before a recommendation of surgical repair.

Summary

A case of anterolateral papillary muscle necrosis is presented. The "standard" clinical and electrocardiographic features of papillary muscle infarction with dysfunction and papillary muscle rupture are described and contrasted with the changes observed. The difficulty of distinguishing between these two entities is discussed.

REFERENCES

1. Adicoff, A., Alexander, C. S., Ferguson, J. N., and Kelly, W. D.: Surgical repair of ruptured papillary muscle complicating posterior myocardial infarction, Amer. J. Card., 11:246, February 1963.

2. Burch, A. E., De Pasquale, N. P., and Phillips, J. H.: Clinical manifestations of papillary muscle dysfunction, Arch. Int. Med., 112:112, July 1963.

3. Case records of the Massachusetts General Hospital, N. Engl. J. Med., 270:98, 9 January 1964.

4. Holloway, D. H., Whalen, R. E., and McIntosh, H. D.: Systolic murmur developing after myocardial ischemia or infarction, J.A.M.A., 191:888, 15 March 1965.

5. Orlando, M. D., Wooley, C. F., Scarpelli, D., and Ryan, J. M.: Mitral regurgitation caused by infarcted papillary muscles: Report of fifteen cases, abstracted, Circulation, 30:111-136, 1964.

6. Payne, W. S., Hunt, J. C., and Kirklin, J. W.: Surgical repair of ventricular septal defect due to myocardial infarction, J.A.M.A., 183:603, 16 February 1963.

7. Phillips, J. H., De Pasquale, N. P., and Burch, G. E.: The electrocardiogram in infarction of the anterolateral papillary muscle, Am. Heart J., 66:338, September 1963.

8. Phillips, J. H., Burch, G. E., and De Pasquale, N. P.: Syndrome of papillary muscle dysfunction: Its clinical recognition, Ann. Int. Med., 59:508, October 1963.

9. Robinson, J. S., Stannard, Mary M., and Long M.: Ruptured papillary muscle after acute myocardial infarction, Am. Heart J., 70:233, August 1965.

Glutethimide Intoxication

With Prolonged Coma
And Hyperpyrexia Treated with
Methylphenidate

L. A. SCHLEISSNER, M.D., *Torrance*

GLUTETHIMIDE (Doriden®) is the sixth most commonly prescribed hypnotic in this country,[9] and intoxication due to ingestion of this drug with suicidal intent is relatively frequent. Narcosis and often death occur when the glutethimide blood level reaches 2 to 3 mg per 100 ml.[9,7,11] The severity of the clinical condition may be aggravated by alcohol and other depressants.[2,11]

The course of the intoxication is progressive, beginning with lethargy and confusion and continuing to garbled speech, flushed face, coma, total flexor paralysis and, finally, respiratory and circulatory collapse.[12]

This report deals with an attempted suicide with glutethimide, with the unusual features of prolonged coma (120 hours) and hyperpyrexia, treated successfully without hemodialysis.

Report of a Case

A 45-year-old white man was brought to the hospital by his estranged wife on 19 September 1964 after she had found him in a comatose condition in her home. The patient had been under psychiatric care for the past two years. He had

---

From the South Bay Hospital, Redondo Beach, and the University of Southern California School of Medicine, Los Angeles.

Submitted 7 February 1966.

Reprint requests to: 21350 Hawthorne Boulevard, Torrance, California 90503 (Dr. Schleissner).

come to his wife's home the preceding evening for some discussion, after having been separated from her for more than a year. The wife could give no information regarding the amount and nature of the drug ingested, other than that she thought he had taken the suicidal dose about 10 hours before admission.

The patient had been entirely well physically except for occasional bouts of spastic bowel. The blood pressure on admission to hospital was 120/80 mm of mercury and the pulse rate was 92 per minute and regular. Respirations were 32 per minute and shallow. Rectal temperature was 37.6°C (99.6°F). The patient was comatose and did not react to painful stimuli. The pupils were fixed and constricted. Deep tendon and corneal reflexes were absent, but the gag reflex was present. Breathing was labored and the patient was perspiring profusely. The initial clinical impression was coma due to barbiturate intoxication.

The stomach was lavaged and analysis of the contents indicated no barbiturates or salicylates were present. The blood level of barbiturates was 0.8 mg per 100 ml. A request was made for a determination of the blood level of glutethimide but the test was not obtained that day. Several episodes of apnea occurred and an endotracheal tube was inserted and connected to a Bird respirator.

The next day the patient was still comatose but the pupils reacted sluggishly to light. The carbon dioxide combining power was 22 mEq per liter.

On the third hospital day, determination of the glutethimide blood level was again requested. The carbon dioxide combining power was 26.2 mEq per liter. Clinically the patient appeared unchanged. The pupils were large and reflexes were completely absent. Later that day tracheostomy was performed because of increasing difficulties with the endotracheal tube. Many coarse rales in chest developed. The rectal temperature was 39.4°C (103.0°F). Respiratory difficulties continued and administration of methylphenidate (Ritalin®), 30 mg intramuscularly every half hour, was begun, with careful observation for signs of excessive stimulation. After adequate bronchial toilet, the lungs appeared clear to percussion and auscultation.

The next morning the rectal temperature was 40.6°C (105.0°F) and cooling measures were begun. The patient was given adequate amounts of fluid and electrolytes intravenously. Hourly urinary output was always satisfactory and the specific gravity of the urine was normal. When the report on the blood glutethimide level showed it to be 2.8 mg per 100 ml, hemodialysis was considered, but the chief physician in charge of the nearest hemodialysis unit felt that the blood glutethimide level at this time was not high enough to warrant its use, and he recommended continued conservative care. The dosage of methylphenidate was increased to 50 mg intramuscularly every half hour. An x-ray film of the chest taken with a portable unit did not show any significant pulmonary infiltration.

On the fifth day cultures of material that drained from the tracheostomy tube grew coagulase-positive Staphylococcus aureus. Administration of methicillin was started, 1 gm intramuscularly every six hours. A blood culture was negative for pathogenic organisms.

The patient had several severe shivering spells and the high temperature continued. At one time the rectal temperature was 41.9°C (107.3°F) in spite of the use of two hypothermic blankets. An x-ray film of the chest showed no change from the one taken previously.

On the sixth day the patient finally responded to painful stimuli and the administration of methylphenidate was discontinued, after a total of 1,050 mg had been given. Later that evening, however, the patient again became unresponsive, and methylphenidate therapy was resumed. The drug was finally discontinued on the seventh day, after another 500 mg had been given.

From this point onward, the patient gradually emerged from the comatose state which had persisted for five days. On the seventh day, also, profuse bleeding began from the tracheostomy incision and from the cut-down sites on the arm. The platelet count and the Lee-White clotting times were both within normal limits but the prothrombin time was 17 seconds (control 12 seconds), indicating prothrombin activity of 39 per cent.

The patient continued to improve, although the temperature remained high, with readings of 40°C (104°F) and 46.0°C (105°F) recorded during the day. For his still precarious condition, he was transferred to a local Veterans Administration hospital. The hyperpyrexia continued for several more days without evidence of significant infection anywhere.

When the patient appeared to have recovered fully, a detailed psychiatric examination did not reveal any sign of intellectual or memory impairment. He freely said that he had taken handfuls of the Doriden® tablets to end his life. However, he still appeared emotionally unbalanced and was judged potentially suicidal by the examining psychiatrist. He was transferred to the psychiatric ward of the hospital but he promptly left, against medical advice. After several weeks of rest at home, he resumed his previous occupation.

Seven months later, the patient made another suicide attempt, again by ingesting an overdose of glutethimide. There was much less central nervous system depression in this attempt, but the rectal temperature rose to 40°C (104°F) for a seven-hour period, beginning 30 hours after ingestion of the drug. He was treated only with parenteral fluids and intermittent oxygen by mask, and recovered completely.

Comment

Irvine and coworkers[6] reviewed the world literature and placed the overall mortality of glutethimide intoxication at 24 per cent. It has also been stated that the duration of glutethimide-induced coma in non-fatal cases is from 36 to 72 hours,[12] and that respiratory depression and apnea are seen only rarely in non-fatal cases.[8] Both respiratory depression and apnea developed in this case. The longest duration of coma in the patients reported by Maher and associates[8] was 120 hours—the same as in the patient reported here.

Frequently in patients who have taken large amounts of glutethimide, abundant, tenacious tracheobronchial secretions lead to pulmonary congestion and pneumonia. It is mandatory to maintain an adequate airway and to give oxygen therapy.[12]

Patients with glutethimide-induced coma not uncommonly relapse after initial response to therapy. This has been explained by the relative insolubility of the drug in the gastrointestinal tract,[12] which makes reabsorption possible when intestinal activity is resumed as the coma lightens. Relapse occurred in the patient here reported upon, and treatment with methylphenidate had to be resumed.

Two unusual clinical features of this case of glutethimide intoxication deserve mention. One is the persistence and extent of hyperpyrexia, which began on the third day of coma, at times exceeding 41.7°C (107°F) rectally, and lasted for several days after the patient emerged from coma. This drug fever has been ascribed by Maher and associates[8] to a central (hypothalamic) mechanism. Only one of the patients observed by them had fever as high as was recorded in the present case. Zivin and Shalowitz[13] report two cases of drug fever as high as 38.9°C (102°F), but it was believed to be a toxic reaction to prolonged administration of glutethimide, not a result of overdosage.

The second unusual feature is the apparent bleeding tendency in this patient, judged by the prolongation of the prothrombin time. Two of the patients reported by Maher and associates[8] also had prolonged prothrombin time. One of these patients also had a low platelet count, but the platelet count was normal in the patient reported upon here.

Patients with a glutethimide blood level of less than 1 mg per 100 ml can be treated symptomatically.[8,11,12] If the blood level is less than 3 mg per 100 ml but deep coma is present, Maher and associates[8] rely on central nervous system stimulation with bemegride (Megimide®) or with other central nervous system stimulants. Only if glutethimide blood levels are over 3 mg per 100 ml is hemodialysis thought mandatory.

In the present case the patient was treated with large doses of methylphenidate (a total of 1,550 mg). No evidence that methylphenidate may cause hyperpyrexia has been found in the literature. The effectiveness of this drug in the pharmacologic treatment of coma of diverse origin has recently been reemphasized by Hoagland.[5] Peritoneal dialysis has been mentioned favorably by some observers,[1,4] but disparaged by others[3,10] as being ineffective due to the slow rate of exchanges produced.

Maher and associates[8] said that prolonged coma in itself may be indication for hemodialysis. The role of methylphenidate in the present case is difficult to assess. The large doses employed had no harmful effects and possibly enabled the patient to recover without hemodialysis, in spite of the prolonged coma and the significant blood level of glutethimide (2.8 mg per 100 ml) reported on the fourth hospital day (and assumed to have been much higher earlier).

Summary

A 45-year-old man, after taking an overdose of glutethimide (Doriden®) remained in coma for five days. Tracheostomy and assisted respiration were required because of respiratory embarrassment from retained secretions with ensuing respiratory depression, and finally apnea. Primary ther-

apy consisted of large doses of an analeptic agent, methylphenidate (Ritalin®). Unusual features of the clinical course were hyperpyrexia (as high as 41.9°C by rectum) which persisted several days after the coma subsided, and an apparent bleeding tendency with a prolonged prothrombin time. In spite of the prolonged duration of coma and the degree of hyperpyrexia, the patient survived without resort to hemodialysis and without residual ill effects.

Generic and Trade Names of Drugs

Glutethimide—*Doriden.*
Methylphenidate—*Ritalin.*
Bemegride—*Megimide.*

REFERENCES

1. Barbour, B. H.: Peritoneal dialysis in the management of dialysable poisonings, Clin. Res., 8:114, January 1960.
2. Bordeleau, J. M., Domingue, C., and Auzepy, P.: Intoxication par la glutethimide (Doriden®), Un. Med. Canada, 85:676-680, June 1956.
3. Del Greco, F., Arieff, A. J., and Simon, N. M.: Acute barbiturate and glutethimide intoxication, Quart. Bull. Northw. Univ. Med. Sch., 36:306-315, Winter 1962.
4. Ellis, K. G., Lea, R. G., and Drysdale, R. D.: Peritoneal dialysis, Canad. Med. Assn. J., 88:928-931, 4 May 1963.
5. Hoagland, R. J.: Pharmacologic treatment of coma of diverse origin, Amer. J. Med. Sci., 249:623-635, June 1965.
6. Irvine, R. O. H., Montgomerie, J. Z., and Spence, M.: Assisted respiration, noradrenaline infusion and the artificial kidney for glutethimide (Doriden®) poisoning, Med. J. Aust., 2:277-279, 17 August 1963.
7. Kier, L. C., Whitehead, R. W., and White, W. C.: Blood and urine levels in glutethimide intoxication, J.A.M.A., 166:1861-1866, 12 April 1958.
8. Maher, J. F., Schreiner, G. E., and Westervelt, F. B., Jr.: Acute glutethimide intoxication, Amer. J. Med., 33:70-82, July 1962.
9. McBay, A. J., and Katsas, G. G.: Glutethimide poisoning: A report of four fatal cases, N. Engl. J. Med., 257:97-100, 18 July 1957.
10. McDonald, D. F., Greene, W. M., Kretchman, L., and O'Brien, J.: Experiences in acute glutethimide (Doriden®) intoxication, Invest. Urol., 1:127-133, September 1963.
11. Schreiner, G. E., Berman, L. B., Kovack, R., and Bloomer, H. A.: Acute glutethimide (Doriden®) intoxication, A.M.A. Arch. Intern. Med., 101:899-911, May 1958.
12. Smith, B. E., and Pinto, D. M.: Glutethimide (Doriden®) therapy and overdosage, U.S. Armed Forces Med. J., 11:161-166, February 1960.
13. Zivin, I., and Shalowitz, M.: Acute toxic reaction to prolonged glutethimide administration, N. Engl. J. Med., 266:496-498, 8 March 1962.

Management of Chronic Renal Failure

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. HARVEY G. LAPIDES*: The patient is a 55-year-old Negro woman who was admitted to the hospital with chief complaint of severe pain in the left side of the chest, radiating to the right arm and accompanied by nausea and vomiting. She denied diaphoresis or dyspnea at this time. Fourteen years previously diabetes mellitus and hypertension were discovered and the patient was maintained on reserpine and chlorpropamide until the present admission. Three years before admission, she was first seen in the outpatient department and over the next two and a half years there were episodes of recurrent pyelonephritis, angina, postural hypotension and loss of weight. During that period, the packed cell volume fell from 37 to 22 per cent and serum creatinine rose from 4.3 to 10 mg per 100 ml. She had had persistent proteinuria and the creatinine clearance was 10 ml in one minute. At one point, the serum carbon dioxide was 18 mg and serum calcium 7 mg per 100 ml.

On admission, the patient was in acute distress. The blood pressure was 170/90 mm of mercury. The pulse rate was 80 and regular. On funduscopic examination grade III retinopathy was noted. The lungs were clear. Cardiomegaly was noted and a grade III (in a range of VI) pansystolic murmur was heard maximally at the apex with radiation to the axilla. The number of leukocytes was within normal range. Packed cell volume was 26 per cent. The red blood cell indices revealed hypochromia and microcytosis. A guaiac test of the stool was negative for blood. The urinalysis revealed 3+ protein content and specific gravity of 1.013. A culture of urine grew 15 million colonies per ml of *Aerobacter aerogines,* and E. coli grew on a sputum culture. Other laboratory data were as follows: Creatinine, 12.4 mg per 100 ml of blood; sodium 145 mEq, potassium 6.7 mEq, carbon dioxide 11.5 mEq and chloride 111 mEq per liter. Serum iron was 32 mcg per 100 ml with total iron combining capacity of 268. Serum electrophoresis and cholesterol were within normal limits. Stools were persistently negative for occult blood. Blood sugar two hours postprandial was 177 mg per 100 ml.

On admission, a 1 gm sodium and 30 gm protein diet was prescribed and she was treated with digoxin, chlorpropamide and alphamethyl DOPA. In the first eight hours following admission, she received 70 mEq of sodium bicarbonate and thereafter for eight days was given 3 gm of sodium bicarbonate a day intravenously. On the eighth hospital day, she had two grand mal seizures, each lasting about two minutes, for which she was treated with intravenous glucose, diphenylhydantoin and calcium chloride. At this time, blood carbon dioxide was 30.1 mEq per liter and calcium content following a seizure was 5.5 mg per 100 ml. Following this, alkalinization was discontinued and the patient began to improve. She was given two units of whole blood when the packed cell volume fell to 21 per cent. She was discharged with prescription of digoxin, tolbutamide, alphamethyl DOPA, ferrous gluconate and nitroglycerin. Serum carbon dioxide at the time of discharge was 20.8 mg, creatinine 9 mg and potassium 5.4 mg per 100 ml.

---

*Intern in the Department of Medicine.

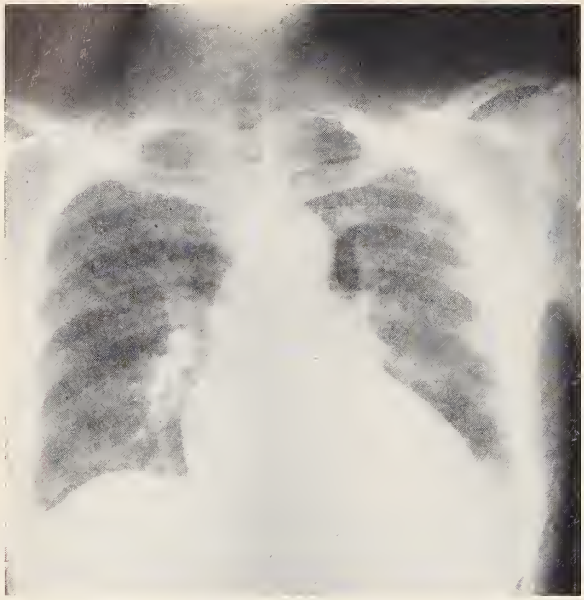


Figure 1.—X-ray film of chest shows cardiac enlargement and increase in size of vessels on both sides. No pleural effusion noted but signs were suggestive of early congestive heart failure.

DR. WARREN RUSSELL*: An x-ray film of the chest (Figure 1) demonstrated cardiomegaly and the vessels were increased in size bilaterally. There was no pleural effusion but the signs were suggestive of early congestive heart failure. An intravenous pyelogram (Figure 2) demonstrated very faint visualization of the urinary collecting structures bilaterally in spite of a double dose of contrast medium. Interestingly, the fourth lumbar vertebra appeared quite dense compared with the remaining vertebral bodies.

DR. FRANK A. GOTCH†: By way of brief introduction into this subject, I would like to make a few general comments about the entity of chronic renal failure. The course of renal failure is extremely variable and there are certainly patients who pass through a long period of chronic renal insufficiency requiring virtually no help. But in many other instances it becomes an increasingly more complex illness that requires a more and more complex therapeutic structure, which in the end often fails. There is one general comment about this which I would like to stress: Chronic renal failure tends to evoke a great deal of pessimism by physicians and the reaction is somewhat analogous to that which physicians often experience when dealing with a patient who has malignant disease. There are several reasons for this. The ability to quantitate renal function with clearance techniques allows the inexorable progression of the disease to be readily apparent in many instances. Second, there is still very little that can be done about the underlying disease process in the kidney, particularly chronic glomerulonephritis and chronic pyelonephritis. What I meant to stress is this: There are reversible features of chronic renal disease which are often overlooked because of pessimism.

With respect to more specific considerations, the patient in the present case illustrates a number of the major problems in medical management of chronic renal failure which I would like to discuss. She had been treated for chronic renal failure as an outpatient for two and a half years and had underlying diabetes and recurrent pyelonephritis. She was admitted because of angina and the possibility of a myocardial infarction. There are several interesting features of this patient's illness that are common in chronic renal failure. With regard to the etiologic factors of angina in this case, the patient had diabetes and hypertension—and these are acceptable reasons for her to have arteriosclerotic heart disease. However, in association with chronic renal insufficiency, progressive ane-

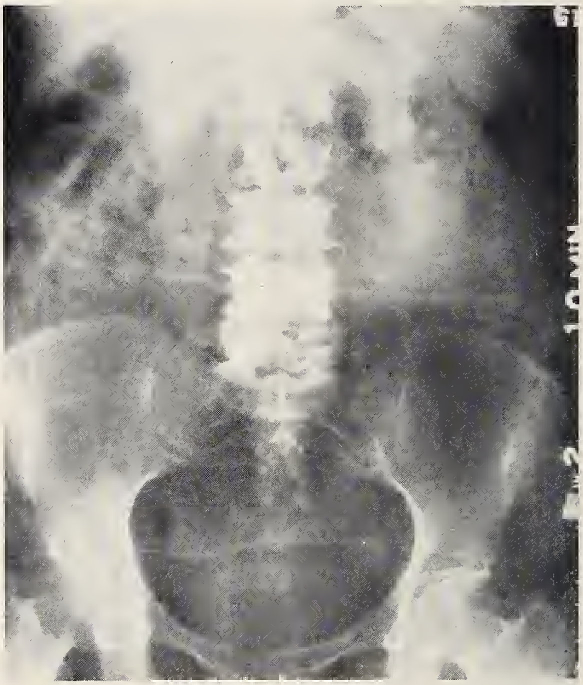


Figure 2.—In an intravenous pyelogram, urinary collecting structures were faintly visualized despite use of double dose of contrast medium. Fourth lumbar appears dense as compared with the other vertebral bodies.

---

*Assistant Professor of Radiology.

†Associate Clinical Professor of Medicine.

mia developed and the packed cell volume fell from 37 to 22 per cent. Anemia is characteristic at some stage in the progression of chronic renal insufficiency. Generally among the etiologic factors there is a combination of marrow depression and accelerated destruction of blood, the intensity of anemia being extremely variable from patient to patient. Once renal insufficiency becomes far advanced, some patients may need a unit of blood every month or every six weeks. Other patients have much more accelerated blood demands and there are occasional patients who need transfusion more often.

As to the treatment of the anemia of renal insufficiency, there are no hematinics that are of any value in this disease. Usually an attempt is made to keep the packed cell volume between 25 and 30 but this is by no means absolute, and in some chronic hemodialysis centers, blood is withheld until the packed cell volume reaches 20 per cent. It is undesirable to transfuse blood to the point that the hematocrit is in normal range, since this may produce a further fall in glomerular filtration rate. The decision between packed cells and whole blood is fundamentally a matter of whether or not there is associated heart failure.

The second point of interest in the patient's history in the present case is the chlorpropamide therapy. This is one oral hypoglycemic agent which is dependent entirely upon renal excretion and for that reason it is a dangerous drug in patients with chronic renal failure; blood levels of the drug may become abnormally high, leading to hypoglycemia.

The final point concerns the primary cardiac lesions that may arise from renal insufficiency itself. Generally, hypertension accompanies chronic renal insufficiency, and hypertensive and arteriosclerotic heart disease are the commonest varieties of associated organ injuries. Pericarditis of course is not uncommon and may occur with minimal azotemia. That is, there are a significant number of patients in whom painful pericarditis develops, with blood urea nitrogen of 60 or 70 mg and creatinine of 5 to 6 mg per 100 ml. More often pericarditis is associated with more severe degrees of azotemia. Pericarditis has occurred in patients on chronic hemodialysis programs where good control of renal failure is accomplished. The third cardiac lesion which may occur with chronic renal failure is perhaps an equivocable one—namely, uremic myocarditis. I am convinced that there is such an entity, since some patients may have severe disabling heart disease which cannot be explained by hypertension. There is no gross evidence of a cholesterol disturbance. In any event, heart failure from these various causes is a frequent concomitant of chronic renal insufficiency.

The next point emphasized by the course of disease in the present case is the rate of progression of renal failure in patients with chronic renal disease. In diabetes, this is a very slow process. The serum creatinine continues to rise slowly over a number of years. It is extremely important in coping with the multiple problems that these patients present to know how rapidly renal insufficiency is developing. There are a number of intercurrent illnesses which may punctuate the course of renal insufficiency and produce a rapid change in serum creatinine, suggesting that an extrarenal process has caused an acute deterioration of renal function. It should be emphasized that the serum creatinine is exponentially related to the glomerular filtration rate. In chronic renal insufficiency, minimal loss in filtration rate produces very large changes in the serum creatinine. Hence, the serum creatinine may rise considerably with only a tiny decrement of glomerular filtration rate that could readily result from the advent of heart failure or salt depletion.

Another point illustrated in the present case is the problem of acid-base regulation and sodium metabolism in patients with chronic renal insufficiency. The most common acid-base disturbance of renal insufficiency (although by no means the only one) is metabolic acidosis; and respiratory alkalosis or metabolic alkalosis may at one time or another complicate the course of the disease. This patient I believe had at least two acid-base disorders—metabolic acidosis and, later, metabolic alkalosis. She had metabolic acidosis when first observed, and subsequently had elevated plasma bicarbonate concentration. The basic cause for the metabolic acidosis is inability to secrete hydrogen ions in the urine and to maintain a normal plasma bicarbonate concentration. In most patients who are reasonably stable, a steady state is reached because of the decreased daily production of hydrogen ion as a consequence of anorexia, limited protein intake, lowered catabolism, and nutritional failure. These factors frequently reduce the daily hydrogen ion production from a normal level of 75 mEq per 24 hours to as low as 10 or 20 mEq per 24 hours. Thus, patients with chronic renal failure have a decidedly reduced daily load of hydrogen ion to be excreted. Consequently, with some reduction in the plasma bicarbonate level they are able to get along quite well.

Using the plasma bicarbonate level as an index of the metabolic acidosis, levels of 15 or 16 are extremely well tolerated; and at present there is really no evidence that one should treat this. The main reason to treat acidosis in renal insufficiency is the advent of subjective dyspnea in order to maintain appropriate respiratory compensation for a lowered plasma bicarbonate level. It is undesirable, therapeutically, to bring about a rapid rise in the plasma bicarbonate. A rule of some help is that the administered bicarbonate will be distributed in about 40 per cent of the body weight. Thus, the body weight in kilograms multiplied by 0.4 can then be multiplied by the change in plasma bicarbonate one wishes to achieve with alkalinizing therapy as a first approximation of how much bicarbonate to administer. The goals should certainly be partial correction of the acidosis, but never full correction; for with full correction, muscular irritability increases and a convulsive problem may ensue.

The patient presented received 3 gm of sodium bicarbonate or 35 mEq of sodium bicarbonate per 24 hours. This accumulated over an eight-day period so that a positive alkali balance resulted with a progressive rise in the plasma bicarbonate concentration. The grand mal seizure may have resulted, in part, from this metabolic alkalosis.

Related to the acid-base problem is the problem of sodium and water regulation in chronic renal insufficiency. Patients with chronic renal failure frequently have mild sodium-wasting and should not have sodium restriction. Rigid sodium restriction may be necessary if there are coexisting severe heart failure and hypertension. Whenever severe sodium restriction is employed, the patient must be observed carefully to avoid the problem of salt depletion which will lead to predictable consequences, particularly a falling glomerular filtration rate. If in the presence of severe acidosis there is a decided limitation in the amount of sodium one can administer, calcium lactate or calcium citrate may be used as alkalinizing agents. This has another desirable effect, in that hypocalcemia is almost always present. The disposable anion of these compounds will become bicarbonate so that one has a pathway of producing some alkalinization without the addition of sodium ion if sodium restriction is absolutely essential.

Phosphorus metabolism may also present problems in these patients. Hyperphosphatemia will supervene whenever the glomerular filtration rate falls below 20 ml per minute. Moderate dietary phosphorus restriction and adequate amounts of aluminum hydroxide gels usually restore the serum phosphorus and calcium to near normal levels at any stage of chronic renal failure. It should be emphasized that certain antacid compounds contain sizable quantities of magnesium and are to be avoided because use of them may lead to serious hypermagnesemia. The problem of hyperkalemia in chronic renal insufficiency is not generally a very serious one in patients who do not have oliguria. It should be mentioned that diets which are designed to be low in sodium frequently are very high in potassium, so that with significant hyperkalemia in a patient with chronic renal failure without oliguria, some evaluation of the dietary potassium content should be made.

I will now turn to the question of chronic hemodialysis and how this technique fits into the management of patients with chronic renal failure. This has attracted a great deal of attention and controversy. It should be strongly emphasized that with the optimal techniques now available, dialysis with the artificial kidney twice weekly for 12 to 16 hours in a patient with end-stage renal disease maintains a creatinine clearance of about 5 to 10 ml per minute. But with dialysis carried out only twice weekly, the cumulative balances of sodium, water, potassium, phosphorus and hydrogen accumulate in the intervals. The anemia of chronic renal failure is not corrected by hemodialysis and patients continue to require blood transfusions.

The procedure achieves only partial control of the nutritional status of the patient. The nutritional status of most patients remains at the level one might expect with moderately well controlled chronic renal failure. There is unfortunately uncertainty in the control of the secondary organ lesions. Peripheral neuritis has become recognized as one of the severe complications of chronic renal insufficiency with the advent of techniques to continue life far longer than had been possible in the past. This neuritis can develop in the course of chronic hemodialysis although it is usually fairly well controlled by dialysis therapy. Therefore, the therapeutic results of hemodialysis are as follows: It achieves a lesser degree of chronic renal failure that is compatible with life for a long period of time; patients must continue on rigidly controlled diets; they have variable malnutrition, variable progression of secondary organ lesions, and variable rehabilitation to work.

The magnitude of the problem of chronic hemodialysis is illustrated by the fact that the number of patients appearing annually in the United States with chronic renal insufficiency is approximately two thousand. Approximately a hundred or a hundred and fifty patients are being treated in all of the centers now undertaking chronic hemodialysis. The annual cost at optimal conditions has been estimated at $5,000 each. At the San Francisco General Hospital, our calculations indicate a minimum cost of $25,000 a year in our circumstances.

In conclusion: Chronic hemodialysis cannot play any significant role in the thinking of a physician as far as the management of his own patients with chronic renal insufficiency is concerned.

MANAGEMENT OF CHRONIC RENAL FAILURE

Recent Summaries in the Literature

A. General Medical Management

1. Seldin, D. W., Carter, N. W., and Rector, F. C.: "Consequences of Renal Failure and Their Management" in Diseases of the Kidney, Strass, M. B., and Welt, L. G., Editors, Little, Brown and Co., chapter 5, 1963.

2. Levinsky, N. G.: Current concepts: Management of chronic renal failure, New Engl. J. Med., 271:358-360, 460-463, 1964.

3. Merrill, J. P.: Management of chronic renal failure—present and prospective, Amer. J. Med., 36:763, 1964.

B. Intermittent Peritoneal Dialysis in Chronic Renal Failure

1. Gutch, C. F., Stevens, S. C., and Watkins, F. L.: Periodic peritoneal dialysis in chronic renal insufficiency, Ann. Intern. Med., 60:289, 1964.

2. Schumacher, R. R., Ridolfo, A. S., and Martz, B. L.: Periodic peritoneal dialysis for chronic renal failure, Ann. Intern. Med., 60:296, 1964.

3. Boeu, S. T., et al.: Periodic peritoneal dialysis using the repeated puncture technique and an automatic cycling machine, Trans. Amer. Soc. Artif. Intern. Organs, 10:409, 1964.

4. Barry, K. G., et al.: A new flexible cannula and seal to provide prolonged access to the peritoneal cavity for dialysis, Trans. Amer. Soc. Artif. Intern. Organs, 9:105, 1963.

5. Lasker, N., et al.: The management of end-stage kidney disease with intermittent peritoneal dialysis, Ann. Intern. Med., 62:1147, 1965.

C. Intermittent Hemodialysis in Chronic Renal Failure

1. Scribner, B. H., et al.: The treatment of chronic uremia by means of intermittent hemodialysis: A preliminary report, Trans. Amer. Soc. Artif. Intern. Organs, 6:114, 1960.

2. Hegstrom, R. M., Murray, J. S., et al.: Two years' experience with periodic hemodialysis in the treatment of chronic uremia, Trans. Amer. Soc. Artif. Intern. Organs, 8:266, 1962.

3. Scribner, B. H.: Discussion, Trans. Amer. Soc. Artif. Intern. Organs, 10:189, 1964. (Reference to Scribner's verbal report of five year survivals on intermittent hemodialysis.)

4. Schupak, E., and Merrill, J. P.: Experience with long-term intermittent hemodialysis, Ann. Intern. Med., 62:509, 1965.

5. Freeman, R. B., Maher, J. F., Schreiner, G. E., et al.: Hemodialysis for chronic renal failure. I. Technical considerations. II. Biochemical and clinical aspects. III. Medical, moral and ethical, and socioeconomic problems. IV. Psychological considerations. Ann. Intern. Med., 62:519, 1965.

California
Medicine

Editor
DWIGHT L. WILBUR, M.D.
•
Assistant to the Editor
ROBERT F. EDWARDS
•
For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MACLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

EDITORIAL

Mandatory Tests for Phenylketonuria

The California Legislature in 1965 passed a bill requiring that all newborns be tested for preventable disorders leading to mental retardation. Soon afterward the State Board of Health adopted regulations carrying out the intent of the legislation with regard to testing for phenylketonuria (PKU), and since the beginning of this year California law has required that all physicians caring for newborn children have an approved test for PKU administered by an approved laboratory before the child leaves the hospital following birth. PKU testing is now mandatory in most states.

Although it is a rare disease, a great deal is now known about PKU. The paper by Cunningham in this issue of CALIFORNIA MEDICINE (page 1) details much of the information of immediate interest to practitioners regarding the diagnosis, treatment and prognosis of this disorder. Aside from the considerable biochemical, genetic, pediatric and other interests that have centered around PKU during the past several decades, a point of major public interest is that this rare form of mental retardation can be prevented. Early diagnosis and treatment is, of course, the key to effective prevention of the otherwise serious and irreversible mental retardation that formerly was characteristic of PKU. Thus, and notwithstanding the major scientific and clinical interests in this disorder, public and professional awareness of the preventable aspects have proved a major stimulus in reaching the present situation of mandatory testing. This is certainly a point of great interest to physicians. In determining how widespread future legislative response to public interest in disease control may become, the history of PKU testing can be taken as an important recent example.

Because all infants born in this state, and a large proportion of California physicians, are involved now in mandatory PKU testing, several technical questions have been raised and have been answered, at least for the present. Points such as the timing of the test relative to the child's age and amount of protein intake, the establishment of a definitive diagnosis of PKU following positive repeat screening tests, and the difficulties inherent in dietary treatment of the disease are being discussed widely in the medical literature. At present the regulations on testing adopted in California are consistent with scientific evidence accumulated nationwide as described in the article on PKU appearing in this issue.

Newborn screening is by no means the only method of controlling PKU or any similar disorder. Some proportion of cases detected in the newborn each year is in babies born to a couple who have already had a child with PKU. Probably less than 15 to 20 per cent of all cases fall into this category; but since this must be considered as pointing to a very high risk, some measure of control of the disorder can be achieved through registration of cases then careful watching of these families for subsequently born affected children. Screening among patients with neurological disorders and mental retardation can likewise add to the numbers of known cases and thus increase the effectiveness of registration and the awareness that other children in such families may be born with the disease.

In spite of the many publications about PKU and the great interest in the disease in the past and at present, a great deal remains to be done. There are already several indications that persistent high blood phenylalanine in the newborn is not necessarily synonymous with the classical disorder of PKU which is associated with inevitable severe mental retardation. Evidence from clinical and population studies is beginning to suggest that PKU may well represent a collection of metabolic disorders, all of which result in high phenylalanine as the single common characteristic. It should be stressed, on the other hand, that at this time there is no way of determining which child, if any, may not be damaged by a persistent elevation of blood phenylalanine. For this and other reasons, diagnosis as early in life as possible, followed by effective treatment, remains the only course of management in this disorder.

ROBERT W. DAY, M.D., Chief Deputy Director
California State Department of Public Health
Berkeley

New Faculty Appointments

Each of the four men appointed 1 July to high administrative posts at the University of California School of Medicine, San Francisco, has had previous administrative experience at that institution.

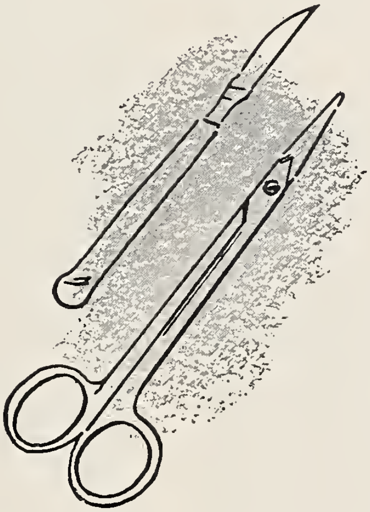
Willard C. Fleming, D.D.S., who was appointed Chancellor for 1966-67, was formerly Vice Chancellor.

Stuart C. Cullen, M.D., who was named Dean of the School of Medicine, was Associate Dean.

Harold A. Harper, Ph.D., the new Vice Chancellor, was Dean of the Graduate Division.

Leslie L. Bennett, M.D., who becomes Vice Chancellor for Academic Affairs, was Acting Vice Chancellor.

We believe that these men, whose record of accomplishment warrants their appointment to a higher place in familiar surroundings, can begin their tasks with good prospect of success. We congratulate them and wish them well.



California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 521st Meeting of the Council, San Francisco, Hilton Inn, 7 May 1966.

The meeting was called to order by Chairman Anderson in the Hilton Inn, San Francisco, on Saturday, 7 May 1966, at 9:15 a.m.

Roll Call

Present were President MacLaggan, President-elect Morrison, Vice-Speaker Telford, Editor Dwight L. Wilbur, Secretary Weyrauch and Councilors Isenhour, Eastman, Todd, Gooel, Taw, Bullock, O'Connor, Ham, Rogers, Crum, Boyle, Burnett, Richard S. Wilbur, Miller, Watts, Fenlon, Kay, Kaiser, Anderson, Yant, Grunigen and Immediate Past President Teall. Absent for cause were Speaker Quinn and Councilors Maguire and Longmire.

A quorum present and acting.

Present by invitation were Messrs. Collins, Thomas, Eberlein, Whelan, Blackley, Clark, Klutch, Hetland, Mrs. Griffith, Doctor Miller, Mrs. Redfern and Miss Price of CMA staff; Messrs. Hassard and Huber, legal counsel, component society executives Scheuber of Alameda-Contra Costa, Rideout of Butte-Glenn, Geisert of Kern, Dalbec of Los Angeles, Collins of Marin, Colvin of Monterey, Dochterman of Sacramento, Donmyer of San Bernardino, Jackson of San Diego, Neick of San Francisco, Thompson of San Joaquin, Wood of San Mateo, Marvin of Santa Barbara, Funk of Solano, Brown of Sonoma, Bruce of Tulare; Messrs. Saylor, Heller, Babb, Humbert and Potloff of California Physicians' Service; Messrs. Salisbury, Putnam and Brown of the Public Health League; Mr. Gould of the AMA; Mr. Layton of AMPAC; Mrs. Gentile, president of the California Medical Assistants Association; Mrs. Stanley, president of the California Nurses Association; Doctors Glaser and Nelson of Stanford University School of Medicine; Doctor Bostick of UC, California College of Medicine; Doctor Tupper of UC at Davis, School of Medicine; Doctor Day, Deputy Director, State Department of Public Health; Doctor Galioni, State Department of Mental Hygiene; Doctor Radl, Medical Director, State Department of Employment; and others.

JAMES C. MACLAGGAN, M.D.	President
JOHN G. MORRISON, M.D.	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH W. TELFORD, M.D.	Vice-Speaker
CARL E. ANDERSON, M.D.	Chairman of the Council
ALBERT G. MILLER, M.D.	Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D.	Secretary
DWIGHT L. WILBUR, M.D.	Editor
HOWARD HASSARD	Executive Director

General Office, 693 Sutter Street, San Francisco 94102 • 776-9400
ED CLANCY . . . . Southern California Office
1515 N. Vermont Avenue, Los Angeles 90027 • 663-8071

1. *Minutes for Approval*

On motion duly made and seconded, minutes of the 519th and 520th meetings of the Council, held 18 to 23 March 1966, were approved as distributed.

2. *Membership*

(a) On motion duly made and seconded, 1,846 members whose dues were delinquent and now paid, were reinstated.

(b) On motion duly made and seconded 39 applicants were voted election to Associate Membership. These were:

Ellen Skillen Alkon, Molly Cholfin, George C. Cunningham, Vera B. Fryling, Frederick B. Hodges, Gilbert J. Roberts, Jr., Richard H. Svihus, Alameda-Contra Costa County; Robert Stewart Peters, Fresno County; Robert W. Chamberlain, Kern County; Marvin E. Royce, Imperial County; Marvin B. Cohen, Delmar Jay Daniel, Jay H. Daniels, Frieda L. Grell, Miles J. O. Gullingsrud, Donovan R. Hare, Harry H. Herbst, Lucille L. Ivan, Irving Krakower, C. Conrad Najjar, Kakuya Nakadate, Lester H. Rhymes, Harry O. Ryan, Joseph Frederick Shea, Jane Shields, Marcelo Ismael Stubrin, John Theodore Tokar, Willis A. Wingert, Los Angeles County; Ernest W. Klatte, Mendocino-Lake County; Glenn W. Koford, Napa County; Herbert I. Cohen, Orange County; John W. Koett, Riverside County; Charles E. Whitcher, Santa Clara County; Stephen E. Cox, Sally Ruth Grimshaw, Sonoma County; Carl D. Shirk, Stanislaus County; Debora Pineles, Tulare County; Conrad N. Ellner, Marin County; and Lester E. Haentschel, Ventura County.

(c) On motion duly made and seconded, 11 members were voted election to Retired Membership. These were:

David C. Wise, Edith P. Wise, Alameda-Contra Costa County; Harry Alban, Leon G. Campbell, Los Angeles County; Ralph B. Coomber, Orange County; Espey F. Cannon, San Bernardino County; Glenn F. Cushman, Karl L. Schaupp, Sigurd von Christierson, San Francisco County; F. Paul McManus, San Mateo County; J. Samuel Staub, Santa Clara County.

(d) On motion duly made and seconded, a reduction of dues was voted for 36 members for reasons of prolonged illness or postgraduate education.

3. *Recognition of Retired Councilor Wilson*

Chairman Anderson gave to Councilor Henry V. Eastman a plaque to present to Doctor Llewellyn E. Wilson, expressing the appreciation of the California Medical Association for his devoted service as Councilor from the Second District, for the years 1961-66.

4. *California Commission for the Accreditation of Nursing Homes*

Chairman Anderson read a letter from Doctor Pierre Salmon, CMA's representative to the recently dissolved California Commission for the Accreditation of Nursing Homes, expressing the gratitude of its Commissioners for CMA's support of the organization's activities.

5. *AMA President James Z. Appel*

The Council welcomed special guest Doctor James Z. Appel, president of the American Medical Association. In his remarks, Doctor Appel praised CMA for leadership in the implementation of Title XIX of P.L. 89-97 in California. He also urged more active participation of California physicians in AMPAC and CALPAC.

6. *Report of the President*

President MacLaggan reported on several meetings he had attended since the last meeting of the Council. Among these was a meeting of the Crippled Children's Advisory Committee, at which the relationship between the Crippled Children's program and the California Medical Assistance Program (Assembly Bill 5) was explored. Doctor MacLaggan also briefly reported on a recent meeting of the California Hospital Association and a special meeting between State officials and a subcommittee of the County Health Officer's Association, called by Mr. Paul Ward, Administrator of the Health and Welfare Agency. Doctor MacLaggan described the latter meetings as an initial step in revamping the relationships among county, state and national governmental health agencies—regarding their operations in California.

7. *Committee for Emergency Action*

As a result of a joint meeting of the CMA Committee for Emergency Action and the Executive Committee of CPS, Doctor MacLaggan presented two recommendations to the Council for their consideration: (a) that CMA put into operation an "Appeals Mechanism" to advise regarding claims which are still in dispute or doubt after going through the regular review channels of CPS and county societies (to be referred to the Commission on Medical Services for action, with the direction that the Commission rely heavily on its committees on Mediation and Fees), and (b) that the CMA sponsor two regional educational meetings primarily for county society professional review committees—to be held 4 June at the Hilton Inn, San Francisco; and 5 June at the Airport Marina, Los Angeles.

ACTION: Voted to accept both recommendations of the Committee for Emergency Action: the establishment of a CMA "Appeals Mechanism" and the holding of two regional informational meetings for county society professional review committees.

8. *Committee on Committees*

Chairman Morrison offered the following nominations, most of them to fill vacancies or to supplement membership on various CMA Commissions and Committees:

Committee on Veterans Affairs—Robert L. Watson, Los Angeles

Committee on Mediation—George Babbin, Sacramento

Committee on Insurance and Prepayment — A. LaMonte Baritell, Oakland

Committee on Rural Health—M. Marlin Clark, Delano

Committee on Environmental Health—John R. Lee, Mill Valley

Committee on Voluntary Health Agencies—Harney M. Cordua, Jr., San Diego

Bureau of Research and Planning—J. Brandon Bassett, Oakland, and G. Roger Ellison, Pomona

Task Force on P.L. 89-97 — Arthur Howard, Fresno

Committee on Cardiovascular Diseases (new)— Harold I. Griffeath, San Francisco, Chairman; Lewis T. Bullock, Los Angeles; George C. Griffith, Los Angeles; David J. New, Modesto.

Southern California Advisory Committee to Selective Service—Nominated Sanford F. Rothenberg, Beverly Hills, and William H. Kern, Los Angeles.

Medical Staff Survey Committee — Richard H. Anderson, Santa Cruz; Samuel T. D. Anderson, San Rafael; Alfred Auerbach, San Francisco; Robert Buckley, Santa Monica; Woodrow W. Burgess, Sacramento; G. Cameron Cray, Palo Alto; Arthur E. Gladman, Oakland; Norman Graff, San Mateo; Frank V. Hoffman, Huntington Beach; Robert E. James, Belmont; Clement O. Juul, Oakland; Seymour Kolko, San Mateo; Melvin M. Lipsett, Berkeley; Jack B. Lomas, Los Angeles; Edward A. Macklin, San Francisco; D. Stewart MacRobbie, Berkeley; Felix H. Ocko, Berkeley; William R. Sheehy, Berkeley; John A. Stroud, Sacramento; Richard L. Sutherland, Oakland; Rudolph B. Toller, Stockton; Albert T. Voris, Belmont.

ACTION: Voted approval of the above nominations and appointments.

9. *1966 House of Delegates Resolutions*

Resolutions by the 1966 House of Delegates as well as several Reference Committee Recommendations were reviewed and recommendations for action or referral to commissions or committees were discussed.

ACTION: Voted to refer 1966 House of Delegates Resolutions and Reference Committee Recommendations (not embodied in resolutions) to various CMA Commissions and Committees for action and study. (These actions are attached and made a part of these minutes.)

10. *Affiliated Organiations and Invited Guests*

Representatives of affiliated organizations, medical schools and departments of state government reported on activities of interest to the Council and the medical profession. No action was required. Among those present were Doctor Robert J. Glaser, dean of the Stanford School of Medicine, who introduced Stanford's new assistant Dean, Doctor Bernard Nelson; Doctor Charles J. Tupper, dean of the UC School of Medicine at Davis; Doctor Warren Bostick, Dean of the UC-California College of Medicine; Doctor Robert Day, deputy director, State Department of Public Health; Doctor Elmer Galioni, State Department of Mental Hygiene; Doctor Robert Radl, medical director, State Department of Employment; Mrs. Mary Stanley, president of the California Nurses Association; and Mrs. Jeanette Gentile, President of the California Medical Assistants Association.

11. *California Physicians' Service (Blue Shield)*

Doctor Richard S. Wilbur, chairman of the board, presented a progress report on CPS activities as fiscal intermediary for the California Medical Assistance Program (A.B. 5). He reported that from 1 March, when CAL-MAP went into effect until 4 May, CPS had received 1,676,000 claims under the program. Doctor Wilbur also briefly discussed the "Medigap" program which CPS is offering as supplemental coverage to Part B, Title XVIII of P.L. 89-97, as well as coverage which CPS will be offering to those persons over 65 who do not wish to participate in the Part B program.

12. *Medical Executives Conference*

Mr. Rueben Dalbec, conference chairman, presented the names of Richard Hansen of Kern County and Joseph Ryan of San Joaquin County, for consideration for membership in the conference.

ACTION: Voted Mr. Richard Hansen and Mr. Joseph Ryan members of the Medical Executives Conference.

13. *AMA Board of Trustees*

Doctor Dwight L. Wilbur, AMA Trustee, reported on current activities of the Board. The board will explore manpower and educational needs of allied health professions and the responsibilities of physicians in these areas. The AMA board also has been directing attention to unity within the medical profession and recently voted to establish an inter-society committee to explore the functional relationship between the AMA and other physician organizations, such as the American College of Surgeons, the American Academy of General Practice, etc. Along these same lines, two representatives of the AMA attended for informational purposes an initial meeting of the Medical Intersociety Council to consider potential relationships of medicine and government.

14. *Compensation for Physicians' Services*

Councilor Boyle presented for Council consideration a statement on Compensation for Physicians' Services, with particular reference to payment of clinical pathologists under A.B. 5. The statement is as follows:

"Long-accepted traditional, ethical and legal determinations indicate that all medical services provided by a physician for patients, whether individually performed by him or provided by him and under his supervision (such as the services of nurses, assistants, technologists) constitute an integral part of the physician's professional service in the practice of medicine.

"The components of services performed by other persons in support of the physician can be identified but cannot be separated from his professional service. Efforts to separate these services by any mechanism or for any purpose will lead to a deterioration of the quality of medical care thus provided.

"The California Medical Association Council endorses these concepts and further advises all third parties, insuring agencies, governmental and nongovernmental agencies, that the CMA cannot accept discrimination between physicians with regard to the identification of professional services, interference in the manner in which these services are provided or in the compensation for these services, and that the Health and Welfare Agency be advised that all physicians' services, including those of clinical pathologists, be compensated on the same basis—of usual, customary and reasonable."

ACTION: Voted approval of the above statement.

15. *Finance Committee*

Chairman Kay briefly discussed the status of CMA employee benefits for illness and partial disability. He also asked that permission be granted to transmit to Sacramento County Medical Society a check for $500.00, for the book, "History of the Medical Society of the State of California."

ACTION: Voted permission to transmit $500.00 to Sacramento County Medical Society.

16. *Committee on Legislation*

Chairman Kilroy commented on the status of various pieces of legislation considered by the Legislature during its Budget and special sessions and pointed out that with the high proportion of "freshman" legislators who will constitute the next State Legislature, the importance of interim committee hearings and reports will be magnified. Mr. Gene Salisbury of the Public Health League staff discussed activities directed toward the election of State Assemblymen and Senators who will promote high quality medical care in the state.

17. *Ad Hoc Committee on Workmen's Compensation*

Chairman Anderson reported that he and Mr. William Whelan, CMA staff, had recently met with Chairman Saunders of the Division of Industrial Accidents to discuss appointments to the new Medical Advisory Committee to the Division. Mr. Whelan reported that representatives of the insurance industry have drafted a petition to use the 1964 *Relative Value Studies* as the basis for physician compensation under the program. He added that the petition had not yet been introduced and may be discussed at a joint meeting between the CMA ad hoc Committee and the insurance industry representatives, scheduled for 6 June.

18. *Task Force on P.L. 89-97*

On behalf of the Task Force on P.L. 89-97, Chairman Teall presented a statement on county/teaching hospitals, to supplement the statement adopted by the Council on 16 January 1966. After discussion and amendment, the following policy statement was voted upon by the Council.

"The California Medical Association has observed with great interest the developments and the impact on physician staff relationships, of payments from CAL-MAP resources for care of patients in county hospitals and medical teaching hospitals.

"There is growing concern that certain limiting patterns of physician staff organization and payment, now developing in some sections of the state, may continue or accentuate the separation of certain CAL-MAP patients in public and teaching facilities.

"Recognizing that multiple avenues of adaptation are being considered, CMA urges that all interested parties now undertake a careful and thoughtful re-evaluation of the objectives and issues, before the limiting patterns which now seem to be evolving become prematurely established in an inflexible mold."

ACTION: Voted approval of the above statement as CMA policy.

Doctor Teall also reported on the 5 May hearing on A.B. 5 regulations, reviewing the oral testimony he had presented on behalf of CMA.

19. *Joint Council to Improve the Health Care of the Aging*

Doctor Pierre Salmon, chairman of CMA's Committee to Improve the Health Care of the Aging, briefly discussed a written proposal that the California Joint Council to Improve the Health Care of the Aging sponsor, organize and direct regional training programs for the implementation of Title XVIII Conditions of Participation for Extended Care Facilities. Doctor Salmon explained that the informational programs, directed to physicians, administrators and other extended care facility personnel, would be conducted in cooperation with the State Department of Public Health and would entail no cost to the Joint Council or its member organizations. CMA's Task Force on P.L. 89-97 had previously considered the proposal and recommended Council approval.

ACTION: Voted to approve the Joint Council's proposed regional training programs, contingent on funds becoming available from other sources.

20. *Commission on Allied Health Professions and Services*

Chairman Grunigen presented a recommendation from the Committee on Other Professions that each U.S. Congressman from California be urged to support H.R. 4809, "Veterinary Medical Educational Facilities Construction Act," by means of letters over President MacLaggan's signature.

ACTION: Voted approval of the recommendations.

Doctor Grunigen also recommended that the California Delegation to the AMA introduce a resolution in the AMA House of Delegates supporting the veterinary school construction act.

ACTION: Voted to refer to the AMA Delegation, requesting that they support the concept.

Doctor Grunigen further recommended that CMA inform the State Legislature of the high regard physicians hold for veterinarians and of CMA's support for changing the State Personnel Board's classification of veterinarians from "agricultural" to "allied health sciences." After being informed that efforts are being made through various means, the Council took no action.

The final recommendation from the Committee on Other Professions was that the CMA adopt a policy statement on nursing education, as requested by the American Nursing Association.

ACTION: Voted that CMA encourage further development of all forms of nursing education, including two-, three- and four-year programs.

21. *Commission on Public Agencies*

On behalf of the Committee on Mental Health, Commission Chairman Miller asked that the Council consider expressing its support of the California Council for Retarded Children in its grant application for establishment and operation of a Medical Health Advisory Board on Mental Retardation, authorizing CMA participation in the activities of the board.

ACTION: Voted to re-refer the proposals to the Commission on Public Agencies for further study and report in more detail.

22. *Commission on Community Health Services*

Chairman Kay requested, on behalf of the Committee on Rural Health, Council permission to implement a proposed plan to utilize externs in summer work on rural health projects.

ACTION: Voted to approve implementation of the program.

Speaking for the Commission, Doctor Kay recommended that the Council take steps to implement House of Delegates Resolution No. 46-65, by authorizing the Commission to take the initiative in establishing a statewide Community Health Council in cooperation with other health organizations and agencies. The initial step would be to explore the feasibility of forming such an organization with other agencies in the state.

ACTION: Voted to authorize the Commission to proceed in exploring the formation of a Community Health Council.

Regarding House of Delegates Resolution No. 73-66, which calls for the CMA to play a more vigorous role in the Interagency Council on Smoking and Health, Doctor Kay recommended that the Scientific Board be asked to develop a position paper on smoking and health for Council consideration, which, if approved, would be used as a guide by CMA representatives on the Interagency Council.

ACTION: Voted to ask the Scientific Board to develop a position paper on smoking and health for Council consideration.

The final item presented for Council consideration by the Commission was a "Proposed Program to Attract Physicians and Members of the Allied Health Professions to Practice in Rural Areas." As explained by Doctor Kay, the plan would begin with a one-day meeting with deans of medical schools in the state.

ACTION: Voted to approve adoption of the proposed plan, contingent on the Commission's staying within its budget in implementation.

23. *Commission on Communications*

Chairman Todd briefly reviewed current Communications activities. He requested Council approval of CMA's encouraging the expansion of "Doctors News Conference," a Bay area TV program, to other areas in the state. Doctor Todd explained that an appropriate sponsor (subject to Council approval) would be sought and that the expansion would be carried out in cooperation with county societies.

ACTION: Voted to approve statewide expansion of "Doctors News Conference," contingent on Council approval of the sponsor.

24. *Staff Report*

Mr. Howard Hassard, executive director, asked that the Council authorize Mr. Lytton O. Hetland, who has assumed the position of controller on the CMA staff, to sign checks on behalf of the Association.

ACTION: Voted to approve requested authorization.

Mr. Hassard brought to the attention of the Council that CMA had no policy with respect to refunding dues of deceased members, and suggested that the following policy be adopted: if death occurs prior to 2 April, total yearly dues would be refunded; if death occurs after 1 April and before 1 July, half of the dues would be refunded; and if death occurs after 30 June, there would be no refund of dues.

ACTION: Voted to adopt the above as CMA policy on refunding dues of deceased members.

25. *New Council Meeting Date*

Chairman Anderson recommended that the Council meeting originally scheduled for 12 November be changed to 29 October, to make the meeting equidistant from the September and December meetings and to provide more time between that meeting and the AMA Convention.

Adjournment

There being no further business to come before it, the meeting was adjourned at 5:30 p.m.

CARL E. ANDERSON, M.D., *Chairman*
HELEN B. WEYRAUCH, M.D., *Secretary*

Referrals of 1966 CMA House of Delegates Resolutions

(Approved by the CMA Council on 7 May 1966)

Resolution	Title	Referral
No. 1-66	Standardization of Hospital Records	Referred to Commission on Hospital Affairs
No. 2-66	Improvements of Scientific Exhibits	Referred to Scientific Board
No. 3-66	Proprietary Visiting Nurses Services	Referred to Committee on Legislation
No. 4-66 & 37-66	Social Security Administration Payment for Medical Reports	Referred to Task Force on P. L. 89-97 and AMA Delegation
No. 5-66; 38-66; 48-66; 49-66; 58-66; 63-66 & 72-66	Physician-Hospital Relationships	Referred to Task Force on P. L. 89-97
No. 6-66	Broader Dissemination of Health Information	Referred to Commission on Communications
No. 7-66	Appointment of Family Physicians to Medical School Faculties	Referred to Liaison Committee to Medical Schools for study and appropriate action
No. 8-66	Parent-Child Relationships	Referred to Committee on School Health for study
No. 9-66	Graduate Training Programs in Family Medicine	Referred to Liaison Committee to Medical Schools for study
No. 10-66	Hospital Based Specialties Contracts	Referred to Task Force on P. L. 89-97
No. 11-66 & 74-66	Medical Insurance for People Over 65	Referred to Board of Trustees, California Physicians' Service, for study
No. 12-66 & 71-66	Opposition to Senate Bill No. 2568	Referred to Committee on Legislation for information and AMA Delegation
No. 13-66	Reporting of Venereal Disease	Referred to Editor, CALIFORNIA MEDICINE and Commission on Communications
No. 14-66; 54-66 & 87-66	Title XVIII B of Public Law 89-97	Referred to AMA Delegation and Commission on Communications
No. 15-66 & 16-66	Reclassification of Marijuana	Referred to Committee on Dangerous Drugs and Committee on Legislation
No. 18-66	Pathologists—Services	Referred to Task Force on P. L. 89-97
No. 19-66	Utilization of Paramedical Personnel	Referred to Liaison Committee to the Medical Assistants Association and Commission on Allied Health Professions and Services
No. 20-66	Payment of Services Rendered by Radiologists	Referred to Task Force on P. L. 89-97
No. 21-66	Ethics Review for Component Societies	Notify Author of procedure for re-introduction at 1967 House of Delegates
No. 22-66	Honorary Membership for Malcolm H. Merrill, M.D.	Recommended personal letter by President to Dr. Merrill
No. 23-66 & 52-66	Military Dependents Medical Care Program	Referred to Committee on Federal Medical Care Programs and AMA Delegation
No. 24-66	Use of Drafted Doctors	Referred to AMA Delegation
No. 25-66	Usual and Customary Fees from Armed Forces Medicare	Referred to Committee on Federal Medical Care Programs and AMA Delegation

Resolution	Title	Referral
No. 26-66	Drafting of Residents	Referred to AMA Delegation and California Advisory Board to the Selective Service System
No. 27-66	Workmen's Compensation	Referred to Committee on Occupational Health and Rehabilitation for study
No. 29-66	Coroner Functions	Referred to Committee on Legislation for action
No. 30-66	Extension of McAteer Bill	Referred to Committee on Legislation
No. 31-66	Indemnification for Closed Panel Patients	Referred to Commission on Medical Services
No. 32-66	Department of Motor Vehicles Questionnaires	Referred to Committee on Automotive and Traffic Safety
No. 33-66	Amendment to Public Law 89-97	Referred to AMA Delegation
No. 34-66 & 46-66	Amendment to Public Law 89-97	Referred to AMA Delegation
No. 35-66	California Physicians' Service Payments	Referred to Board of Trustees, California Physicians' Service
No. 39-66	Segregation in Component Societies	Referred to AMA Delegation
No. 40-66	CMA Candidates Forum	Referred to Committee on Organizational Review and Planning
No. 41-66	Pollution Control	Referred to Committee on Environmental Health
No. 42-66	Responsible Health Care for All	Referred to Commission on Medical Services
No. 43-66 & 17-66	Abortion	Referred to Council for implementation with requests (1) to better acquaint public with the opposing viewpoints on this subject and (2) to invite and support state legislation either by amending A. B. 1305 or by means of a new bill; also referred to Committee on Legislation and Commission on Communications
No. 44-66	California Physicians' Service	Notify author of procedure for re-introduction at 1967 House of Delegates
No. 45-66	California Physicians' Service	Referred to California Physicians' Service
No. 47-66	Hospital Board Members	Referred to Commission on Hospital Affairs and Committee on Legislation
No. 50-66	Medical Self-Help in Schools	Referred to Committee on School Health for study
No. 51-66	Motorcycle Safety	Referred to Committee on Automotive and Traffic Safety
No. 55-66	Government Hospital Utilization Committees	Referred to AMA Delegation
No. 56-66	Channeling of Funds	Referred to Task Force on P. L. 89-97 and AMA Delegation
No. 57-66	Voluntary Accreditation of Health Insurance Plans	Referred to AMA Delegation, Committee on the Role of Medicine in Society and Committee on Organizational Review and Planning
No. 60-66	Continuing Medical Education	Referred to Committee on Continuing Medical Education for study
No. 61-66	Physician Participation in LVN Training	Referred to Committee on Paramedical Personnel
No. 62-66	Medical Diagnostic Procedures by Optometrists	Referred to Commission on Professional Welfare and Task Force on P. L. 89-97
No. 64-66	Joint Commission for Accreditation of Voluntary Health Insurance Plans	Referred to AMA Delegation, Committee on the Role of Medicine in Society and Committee on Organizational Review and Planning
No. 65-66	Usual, Customary and Reasonable Fees	Referred to Task Force on P. L. 89-97 and Commission on Medical Services
No. 66-66	Study Committees for Infant and Maternal Health	Referred to Committee on Maternal and Child Care for action and Committee on Legislation
No. 68-66	Usual Fee A. B. 5	Referred to Task Force on P. L. 89-97 and Commission on Medical Services

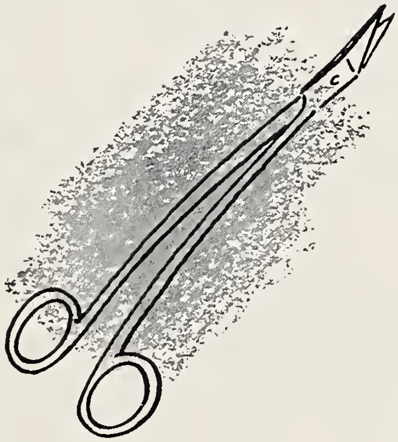
Resolution	Title	Referral
No. 69-66	Hospital-Physician Contractual Arrangements	Referred to Task Force on P. L. 89-97
No. 70-66	Public Law 89-97	Referred to Task Force on P. L. 89-97
No. 73-66	Interagency Council on Smoking and Health	Referred to Commission on Community Health Services for action
No. 76-66	Insurance Assignments	Referred to Task Force on P. L. 89-97 and AMA Delegation
No. 77-66	Direct Patient Billing	Referred to Task Force on P. L. 89-97 and Commission on Communications
No. 78-66	Consultants to AMA Advisory Committee to the Department of Health, Education and Welfare	Referred to AMA Delegation
No. 79-66 & 98-66	Role of Medicine in Society	Referred to Committee on the Role of Medicine in Society for study
No. 80-66	Proposed Rules and Regulations Re: P. L. 89-97	Referred to Task Force on P. L. 89-97
No. 81-66	Usual and Customary	Referred to Task Force on P. L. 89-97 and Commission on Medical Services
No. 83-66	Poison Prevention	Referred to Commission on Community Health Services and Commission on Communications for action
No. 84-66	Medical Libraries	Referred to Council and Committee on Legislation
No. 85-66	Resolution to AMA Re: Function and Activities of Levels of Organized Medicine	Referred to AMA Delegation
No. 86-66	Physician-Hospital Relationships	Referred to AMA Delegation and Commission on Hospital Affairs for action
No. 89-66	Greater Cooperation Between the Medical and Legal Professions	Referred to Liaison Committee to State Bar Association for action
No. 92-66	Implied Consent Law	Referred to Committee on Legislation
No. 93-66	Guiding Principles for Physician-Hospital Relationships	Referred to Medical Staff Survey Committee and Commission on Hospital Affairs
No. 96-66	Agents of Health Care Financing Plans	Referred to Commission on Hospital Affairs and AMA Delegation
No. 97-66	Amendment California Medical Association Bylaws	Notify author of procedure for re-introduction at 1967 House of Delegates
No. 99-66	Medicare Application Question Concerning Subversive Activities	Referred to Task Force on P. L. 89-97 and AMA Delegation
No. 100-66	Commendation to AMA-ERF	Referred to Committee on Organizational Review and Planning and AMA Delegation
No. 101-66; 28-66 & 36-66	Free Choice of Physician	Referred to ad hoc Committee on Workmen's Compensation, Task Force on P. L. 89-97, Commission on Public Agencies and Committee on Organization Review and Planning
No. 103-66	Workmen's Compensation	Referred to ad hoc Committee on Workmen's Compensation
No. 104-66	Physician's Compensation for Administrative Requirements	Referred to Commission on Hospital Affairs and Task Force on P. L. 89-97 for study
No. 105-66	Medical Laboratory Study	Referred to Commission on Community Health Services for action
No. 106-66	"CAL-MED"	Referred to Task Force on P. L. 89-97 by Council action 3/23/66
No. 107-66	Ethical Practice of Anesthesiology	Notify author of procedure for re-introduction at 1967 House of Delegates
No. 108-66	Commendation for Santa Barbara County Physicians	Referred to President for implementation

Referrals of 1966 House of Delegates Reference Committee Recommendations

(Approved by the CMA Council on 7 May 1966)

Reference Committee No. 1

Subject	Referral
Annual Report of California Medical Education and Research Foundation	Referred to California Medical Education and Research Foundation
Information Dissemination by Bureau of Research and Planning	Referred to Bureau of Research and Planning
Reference Committee No. 2	
Informing Membership, Through CALIFORNIA MEDICINE, on Preparation of CMA Budget	Referred to Finance Committee
Cost Estimates on Proposed House of Delegates Resolutions and Unbudgeted Activities Proposed for Council Action	Referred to Finance Committee and Staff
Establishing Committee to Evaluate Proper Role of CMA in Financial Support of Medical Libraries	Referred to Committee on Committees
Placing CMA Income Into Reserves	Referred to Finance Committee
Informing Membership on Need for Dues Increase	Referred to Finance Committee and Commission on Communications



In Memoriam

Burch, Bernard Owen, Livermore. Died 17 May 1966, in Livermore, aged 65, of biliary cirrhosis. Graduate of the University of Michigan Medical School, Ann Arbor, 1929. Licensed in California in 1937. Dr. Burch was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Chamberlain, Robert W., Tehachapi. Died 11 May 1966, in Tehachapi, aged 53. Graduate of the University of Nebraska College of Medicine, Omaha, 1941. Licensed in California in 1948. Doctor Chamberlain was an associate member of the Kern County Medical Society.

✣

Eymundson, Kristbjorn S., San Francisco. Died 22 May 1966, in San Francisco, aged 78. Graduate of Rush Medical College, Chicago, Illinois, 1921. Licensed in California in 1922. Doctor Eymundson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Fletcher, Charles D., San Francisco. Died 13 May 1966, in San Francisco, aged 63, of coronary artery disease. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor Fletcher was a member of the San Francisco Medical Society.

✣

Galt, Curtis Martin, Manteca. Died 10 March 1966, aged 69. Graduate of the University of Nebraska College of Medicine, Omaha, 1922. Licensed in California in 1937. Doctor Galt was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Ingham, Samuel D., Los Angeles. Died 17 February 1966, aged 89, of cerebral thrombosis. Graduate of Medico-Chirurgical College of Philadelphia, Pennsylvania, 1899. Licensed in California in 1920. Doctor Ingham was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Krutchkoff, Morris, San Rafael. Died 24 May 1966, in San Francisco, aged 59. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1931. Licensed in California in 1937. Doctor Krutchkoff was a member of the San Francisco Medical Society.

Kuhlmann, Frederic William, Long Beach. Died 17 January 1966, in Long Beach, aged 73, of pericardial bleeding, myocardial infarction, and arteriosclerosis. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1928. Doctor Kuhlmann was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Lawyer, Paul Carey, Inglewood. Died 4 June 1966, in Inglewood, aged 69, of myocardial infarction. Graduate of the University of Nebraska College of Medicine, Omaha, 1923. Licensed in California in 1924. Doctor Lawyer was a member of the Los Angeles County Medical Association.

✣

Lugosy, Laszlo, Los Angeles. Died 7 June 1966, in Los Angeles, aged 63, of carcinoma of tongue. Graduate of Magyar Királyi Erzsábet Tudományegyetem Orvostudomanyi, Pecs, Hungary, 1930. Licensed in California in 1961. Doctor Lugosy was a member of the Los Angeles County Medical Association.

✣

Miles, Seth Herbert, Los Angeles. Died 29 May 1966, in Los Angeles, aged 76, of bronchopneumonia, carcinoma of lungs. Graduate of Columbia University College of Physicians and Surgeons, New York, New York, 1915. Licensed in California in 1926. Doctor Miles was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Newman, Alfred, San Francisco. Died 20 May 1966, aged 93. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1896. Licensed in California in 1896. Doctor Newman was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Powell, Lyle S., San Diego. Died 1 June 1966, in San Diego, aged 72. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1946. Doctor Powell was a member of the San Diego County Medical Society.

✣

Whitcomb, Edith Lucy, Los Angeles. Died 30 May 1966, in Los Angeles, aged 73, of generalized arteriosclerosis. Graduate of the University of Colorado School of Medicine, Denver, 1926. Licensed in California in 1927. Doctor Whitcomb was a member of the Los Angeles County Medical Association.

Plan to Attend

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS PLUS THREE GENERAL MEETINGS ON THE SUBJECT:

ADVANCES IN DIAGNOSTIC TECHNIQUE

Capability • Reliability • Integration

FIRST CALL FOR

- *Scientific Papers*
- *Medical Motion Pictures*
- *Scientific Exhibits*

★ **If you have a paper** you'd like to present to your colleagues during their section meeting . . . write today to your section secretary (names and addresses of scientific section officers may be found on page 6, Advertising Section of *California Medicine*). Presentations are not limited to Advances in Diagnostic Technique.

★ **If you have a motion picture or exhibit** . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

PLANS FOR THE 1967 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

PUBLIC HEALTH REPORT

LESTER R. BRESLOW, M.D.
Director of Public Health

Plague Warning

BETWEEN THE 14TH AND 17TH centuries, plague was a major threat to the world and in that time it killed an estimated 60,000,000 people, one-fourth of the world's population. Since that time both the incidence of plague and the character of the disease have changed. Long before the introduction of antibiotics, plague had become less of a threat to the world's population, but it is still a serious disease: The mortality rate for bubonic plague, if untreated, is 25 to 50 per cent. In California the last epidemic of plague occurred in 1924. There were 32 cases of the pneumonic form in humans, with 30 deaths.

At present, plague is a disease of wild rodents with very infrequent transmission to man. In the last 10 years there have been four cases in humans in the State, with one death. Infected wild rodents were the source of infection in all cases. The last California case in a human occurred in October in a five-year-old boy.

Periodically plague becomes epizootic in wild rodents in certain areas of the State. Last year the areas so affected were in the Lake Tahoe Region and in Shasta County, leading to the one previously mentioned case in a human. This year epizootic areas have been documented in several counties including Shasta, Lassen, Mono, Madera, Fresno, Tulare, Kern and possibly Kings. It is reasonable to expect that further investigations will reveal other epizootic areas. The animals that have been affected include wood rats, ground squirrels, field mice and chipmunks. Investigations to date indicate that this may be one of the most widespread epizootic infections to occur in California within the past 25 years.

For this reason the State Department of Public Health has issued an order prohibiting trapping, capturing or holding of rodents in areas known to be affected by plague and has revised the provisions of the Administrative Code to tighten existing regulations on the capture and sale of wild rodents. A note has been sent to all local health officers informing them of the epizootic condition and asking them to warn the public to avoid contact with wild rodents, especially any that appear sluggish or are obviously ill or are dead, and to ask anyone who sees animals in that condition to report to the local health officer.

Although it should be kept in mind that even a major epizootic does not necessarily lead to cases in humans, practicing physicians should maintain a high index of suspicion should they see patients with symptoms compatible with plague, especially if there is history of having been in one of the affected areas within the preceding two weeks. Children are more likely than adults to be infected, owing to the greater likelihood of their coming in contact with wild rodents and their ectoparasites.

Systemic manifestations include fever and chills, prostration, delirium, headache, vomiting and diarrhea. Local symptoms classically include lymphadenitis, with enlargement of lymph nodes especially in the groin, axilla or neck. If the disease has spread beyond the bubonic stage and caused septicemia, shock is a frequent finding. Following the septicemic phase, secondary invasion of the lungs by plague bacilli may cause plague pneumonia, a highly contagious and frequently fatal form of the disease.

Diagnosis of plague rests mainly with suspicion of the disease. Confirmation of the diagnosis is established primarily by isolation and identification of the etiologic agent (P. pestis) from clinical material. Additional laboratory procedures are also available for confirmation. These tests can be performed in the laboratories of the State Department of Public Health. Arrangements for shipment of specimens from patients suspected of having plague should be made through the local health department. In any case in which plague is suspected, immediate notification of local health departments and to the State Health Department is essential in the control of this disease.

Streptomycin is the drug of choice in the therapy of plague. However, in recent years it has occasionally proven to be ineffective in some instances. If streptomycin does not bring prompt therapeutic response, either tetracycline or chloramphenicol should be used. If none of these drugs is available, sulfonamides may be effective. Penicillin is not effective in the treatment of plague.

All patients with plague should be put in hospital and isolated. For patients with bubonic plague, ordinary aseptic technique is adequate. An early film of the chest will demonstrate whether or not invasion of the lung has occurred. Although bubonic plague is not ordinarily transmitted from man to man, all contacts should be kept under surveillance for a period of one week. If surveillance is not feasible, chemoprophylactic use of broad spectrum antibiotics in doses of at least 1 gm per day for six days may be necessary. Sulfonamides also may be used for chemoprophylaxis in doses of 2 to 3 gm per day for six days.

In summary, physicians in California should be on the alert for the possibility of an occasional case of human plague resulting from widespread epizootics in wild rodents. It is estimated that the present epizootic may extend for two to three years.

LETTERS *to the Editor*

The Deceptive Acid Phosphatases

IN REFERENCE to the article published in the November 1965 issue of CALIFORNIA MEDICINE by Dr. Jay R. Longley entitled "The Deceptive Acid Phosphatases" (Volume 103, page 343):

While Dr. Longley does all his colleagues a service by pointing up some of the weaknesses inherent in considering elevated prostatic acid phosphatase as an invariable indicator of prostatic carcinoma, some essential considerations were not mentioned in his article. For one thing, Dr. Longley did not identify the microscopic criteria by which prostatic carcinoma was diagnosed in his series. Unless consensus exists as to what *is* and what *is not* prostatic cancer, data cannot be compared from different clinics. Microscopic criteria were designated by Hudson, Finkle, Hopkins, Sproul and Stout in 1954.[1] The pathologist, Dr. Arthur Purdy Stout, of Columbia University College of Physicians and Surgeons in New York, was recently co-author, with Hudson, in an article to appear in the New York State Journal of Medicine (1965) in reference to 1,134 consecutive patients studied by open perineal prostatic biopsy.[2] All diagnoses were made in keeping with their histologic criteria.

In Dr. Longley's paper, he simply stated that "diagnosis was determined by pathologic specimens obtained by perineal or transrectal needle or wedge biopsy, or in the course of prostatectomy, open or transurethral." One cannot gloss over these different sites; the source of the biopsy specimen is exceedingly important. As pointed out by Hudson, Finkle et al., the accuracy of diagnosis of prostatic cancer when specimens are obtained by transurethral resection[3] or by "punch" method[4] is significantly less than with tissue obtained by open perineal prostatic biopsy. Since the posterior surgical capsule of the prostate gland is the most common site of development of prostatic cancer, the best approach for early diagnosis is open perineal prostatic biopsy. Many instances of cancer diagnosed by open biopsy would have been missed if, for example, the transurethral specimen alone had been studied. Thus, Dr. Longley cannot state unequivocally that tissue diagnosed as benign really did not possess a prostatic cancer—unidentified simply because the site of the cancer had not been subjected to biopsy.

Whether inhibitors of prostatic acid phosphatase exist to account for the "errors" cited by Dr. Longley is speculative. In his words, ". . . the large number of false positives, especially in the PAP (prostatic acid phosphatase) in our series and others, has not been explained." Failure to study the site of a prostatic cancer might more likely explain the "false positives" than would inhibiting enzymes to which Dr. Longley alluded.

In an article by Finkle, Ballard, Karg and Smith,[5] it was specified that insufficient change in serum acid phosphataste followed massage of the prostate to provide a "provocative test" of prostatic cancer, as verified by open perineal biopsy. Thus, it is not surprising that Dr. Longley's subjecting some of his patients to "a minimal amount of exercise" in an effort to evaluate changes in serum acid phosphatase provided inconsistent results.

Finally, in a very recent paper, Howard and Fraley[6] cited various causes for elevated serum PAP usually readily differentiated from prostatic cancer. They reported a study of 96 patients amongst whom eight instances of transient elevation of PAP were encountered—due to *prostatic infarction* rather than prostatic cancer. All eight men presented in urinary retention. Serial studies of this serum enzyme revealed rapid decrease; in all these eight patients PAP returned to normal following simple adenectomy. This report, as related to that of Dr. Longley, would point up not only a relatively common, nonmalignant etiology of elevated PAP but also the unpredictable error due to the fortuitous "point in time" at which a single specimen of serum is drawn for study of PAP.

In summary, the focusing of attention on this problem by Dr. Longley is commendable. Additional studies by him and by other investigators are urged.

ALEX L. FINKLE, M.D.

REFERENCES

1. Hudson, P. B., Finkle, A. L., Hopkins, J. A., Sproul, E. E., and Stout, A. P.: Prostatic cancer. XI. Early prostatic cancer diagnosed by arbitrary open perineal biopsy among 300 unselected patients, Cancer, 7:690-703, July 1954.

2. Hudson, P. B., and Stout, A. P.: Prostatic cancer. XVI. Comparison of physical examination and biopsy for detection of curable lesions, New York State Med. J., 1965. (In press.)

3. Hudson, P. B., Finkle, A. L., Trifilio, A., and Wolan, C. T.: Prostatic cancer. IX. Value of transurethral biopsy in search of early prostatic carcinoma, Surgery, 35:897-900, June 1954.

4. Hudson, P. B., Finkle, A. L., Jost, H. M., Trifilio, A., and Stout, A. P.: Prostatic cancer. X. Comparison of open and "punch" biopsy techniques, A.M.A. Arch. Surg., 70:508-512, April 1955.

5. Finkle, A. L., Ballard, J. M., Karg, S. J., and Smith, D. R.: Massage-induced response of serum acid phosphatase related to open perineal prostatic biopsy, J. Urol., 85:829-834, May 1961.

6. Howard, P. J., and Fraley, E. E.: Elevation of the acid phosphatase in benign prostatic disease, J. Urol., 94:687-690, December 1965.

WOMAN'S AUXILIARY

to the California Medical Association

Membership Objectives

THE WOMAN'S AUXILIARY to the California Medical Association was organized at the request of the Medical Association, to complement its organization. The Auxiliary's policies are determined by the CMA. All projects undertaken have been suggested by the Association or have its approval. The Auxiliary objectives parallel those of its parent organization, in all fields except the scientific. Our prime goal is to assist the Medical Association in its program for the best medical care for all.

An important outgrowth of the Auxiliary is the friendly relations and understanding created between physicians' families at local, state and national levels. On the local level, this will enhance a physician's position among his colleagues. Through friendships, it promotes mutual understanding of common problems. A liaison of interest is created between the physician and his wife, through the educational and service programs of both organizations.

The effectiveness of any organization can be measured by the number and type of members it comprises. The larger the Auxiliary, the better it can function in such fields as Community Service, Public Relations and Legislation. As a group, wives of physicians are leaders in their communities, both socially and philanthropically. Since they are in the public eye, they present an image which is associated with medicine. As a member of the Auxiliary, she will be kept informed on all pertinent questions and be able to speak intelligently on such matters. Programs are related to the educational aspects of medicine as well as the social. A well informed physician's wife is an asset to medicine in general and to each physician individually. In the field of legislation alone, the Auxiliary has contributed much to stem the tide of socialized medicine. This is our reason for asking every physician to encourage his wife to join the Auxiliary.

Public Relations and Legislation are not the only fields in which the Auxiliary is active. It has played a major role in Physicians' Benevolence and American Medical Association Education & Research Foundation. Last year the Auxiliary presented over $300,000 to American Medical Association Education & Research Foundation in the belief that medical schools should be maintained by private means rather than reliance on government aid, and that financial problems can best be solved by free enterprise. Taking care of physicians and their wives in time of need is also of major importance. The Auxiliary subscribes to this ideal, and has a committee set up to raise funds for local, state and national benevolence.

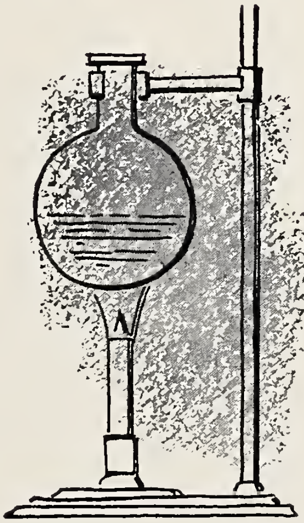
Scholarships for these allied health professions and services are sponsored by the Auxiliary in the form of loans, grants or outright scholarships. Almost every county auxiliary in the United States has such a project. Supplying qualified medical personnel is another instance of promoting free enterprise.

At present, California has the largest State Auxiliary in the nation. However, we cannot be satisfied until our membership almost equals that of the California Medical Association. At present it is just a little over one third of that number. Almost two-thirds of the physicians' wives in California are not associated with the Auxiliary. It is our desire to enroll as many of these women as possible within the next year.

The American Medical Association, Woman's Auxiliary to the American Medical Association, and the California Medical Association have given us the impetus to bridge this gap: They have given support to proposals for joint husband-and-wife membership. This can only be realized with the cooperation of physicians at the county level. We have suggested that each County Auxiliary meet with its local Medical Society and make arrangements for instigation of this program. Through this the wife automatically becomes a member when her husband is accepted into the medical society. To date, this program is being used successfully in some form in 15 counties. By paying your wife's dues, you are insuring her that she belongs and is a part of the total medical picture.

The Auxiliary has always cooperated to the fullest when called upon by the Medical Association. We are eager to assist and we are alert to the problems facing medicine. How better can we serve our husbands and our community than by being affiliated with the Auxiliary, organized especially for us.

Mrs. Robert J. Douds
Membership Committee Chairman



INFORMATION

Sources of Income and Principal Employers Of California Physicians, August 1965

A Report of the Bureau of Research and Planning, California Medical Association

■ *As of August 1965, 54.4 per cent of the 31,551 California physicians in active practice indicated that they receive all of their income from fees-for-service, with another 7.9 per cent receiving at least some of their income in this manner. A total of 8,025 M.D.'s, or 25.4 per cent, are on full-time salaries with no other source of professional income, and the remaining 12.2 per cent are members of group practices, whether on an income sharing or a salaried basis. Almost two-thirds of California physicians (66.6 per cent) consider themselves to be primarily self-employed.*

Of the 21,011 self-employed physicians, 76.3 per cent are in individual practice, 10.5 per cent in partnerships or groups (without income-sharing arrangements) and the remaining 13.2 per cent in group practice (income-sharing). Slightly over one-fifth of all salaried physicians are employed by some Federal agency, primarily in the armed forces. Among the other four-fifths, more than half are hospital employees, with most of the remainder working for other physicians, clinics or educational institutions.

General Practice remains the most heavily populated specialty in California, accounting for 26.3 per cent of all physicians; among self-employed physicians only, G.P.'s number more than one out of every three physicians, or 34.6 per cent. Internists, General Surgeons, Psychiatrists and Obstetrician-Gynecologists rank next in order among all *physicians; however, the positions of Psychiatrists and OB.'s is reversed among* self-employed *physicians.*

DATA DERIVED from AMA physician records provide information about sources of income and the principal employers of physicians in California. At present these data constitute mainly descriptive statistics, since only incomplete earlier data are available for comparative purposes.* They can, however, serve as a basis for analyzing future changes in the composition of California physicians according to these two variables.

As indicated in Table 1a, in August 1965 there were a total of 31,551 physicians practicing in California. Another 2,247 M.D.'s residing in California were either retired or not in medical practice. This latter group is not included among the data shown, since income and employment infor-

---

Reprint requests to: 693 Sutter Street, San Francisco, California 94102.

*See Selected Physician Characteristics in California, as of April 1963, Calif. Med., 99:278-280, October 1963.

TABLE 1a.—*Number of Practicing Physicians in California: Source of Professional Income by Medical Specialty, August 1965*

Medical Specialty	*All Sources of Income*		*Fee-For-Service Only*			*Fee-For-Service + Part-time Salary*			*Full-time Salary + Some Fee-For-Service*				
	No.	*Per Cent*	*Total*	*Individual Practice*	*Partnership or Group*	*Total*	*Individual Practice*	*Partnership or Group*	*Total*	*Individual Practice*	*Partnership or Group*	*Group Practice*	*Full-time Salary Only*
General Practice*	8,299	26.3	6,373	5,657	716	369	294	75	45	38	7	932	580
Anesthesiology	1,257	4.0	797	693	104	26	21	5	24	13	11	184	226
General Surgery	2,642	8.4	1,496	1,287	209	126	100	26	34	28	6	332	654
Internal Medicine	4,272	13.5	1,975	1,720	255	317	260	57	105	87	18	695	1,180
Obstetrics-Gynecology	1,838	5.8	1,114	905	209	74	56	18	28	24	4	289	333
Ophthalmology	984	3.1	664	601	63	55	50	5	12	10	2	110	143
Orthopedic Surgery	1,050	3.3	570	441	129	36	31	5	17	16	1	211	216
Otolaryngology	608	1.9	403	357	46	23	19	4	6	5	1	80	96
Pathology	803	2.5	190	129	61	34	25	9	80	53	27	94	405
Pediatrics	1,677	5.3	786	611	175	72	60	12	54	38	16	302	463
Psychiatry	2,150	6.8	850	827	23	280	242	38	144	129	15	44	832
Radiology	1,157	3.7	411	269	142	77	39	38	42	25	17	292	335
Others with Specialties†	3,745	11.9	1,541	1,318	223	195	155	40	224	189	35	279	1,506
No Specialty Reported‡	1,069	3.4	0	0	0	0	0	0	13	12	1	0	1,056
TOTAL	31,551	100.0%	17,170	14,815	2,355	1,684	1,352	332	828	667	161	3,844	8,025

---

*Includes part-time specialists.
†Includes unlisted specialties as well as sub-specialties of those listed.
‡Includes primarily Interns and Residents.

Note: Excludes 2,247 physicians who are retired and not in practice.

TABLE 1b.—*Per Cent of Practicing Physicians in California: Source of Professional Income by Medical Specialty, August 1965*

Medical Specialty	*All Sources of Income*	*Fee-For-Service Only*			*Fee-For-Service + Part-time Salary*			*Full-time Salary + Some Fee-For-Service*				
		Total	*Individual Practice*	*Partnership or Group*	*Total*	*Individual Practice*	*Partnership or Group*	*Total*	*Individual Practice*	*Partnership or Group*	*Group Practice*	*Full-time Salary Only*
General Practice*	100.0%	76.8%	68.2%	8.6%	4.4%	3.5%	0.9%	0.5%	0.4%	0.1%	11.2%	7.0%
Anesthesiology	100.0	63.4	55.1	8.3	2.1	1.7	0.4	1.9	1.0	0.9	14.6	18.0
General Surgery	100.0	56.6	48.7	7.9	4.8	3.8	1.0	1.3	1.1	0.2	12.6	24.8
Internal Medicine	100.0	46.2	40.3	5.9	7.4	6.1	1.3	2.5	2.0	0.5	16.3	27.6
Obstetrics-Gynecology	100.0	60.6	49.2	11.4	4.0	3.0	1.0	1.5	1.3	0.2	15.7	18.1
Ophthalmology	100.0	65.5	61.1	6.4	5.6	5.1	0.5	1.2	1.0	0.2	11.2	14.5
Orthopedic Surgery	100.0	54.3	42.0	12.3	3.4	3.0	0.4	1.6	1.5	0.1	20.1	20.6
Otolaryngology	100.0	66.3	58.7	7.6	3.8	3.1	0.7	1.0	0.8	0.2	13.2	15.8
Pathology	100.0	23.7	16.1	7.6	4.2	3.1	1.1	10.0	6.6	3.4	11.7	50.4
Pediatrics	100.0	46.8	36.4	10.4	4.3	3.6	0.7	3.2	2.3	0.9	18.0	27.6
Psychiatry	100.0	39.5	38.5	1.0	13.0	11.3	1.7	6.7	6.0	0.7	2.0	38.7
Radiology	100.0	35.5	23.2	12.3	6.7	3.4	3.3	3.6	2.2	1.4	25.2	29.0
Others with Specialties†	100.0	41.1	35.2	5.9	5.2	4.1	1.1	6.0	5.1	0.9	7.4	40.2
No Specialty Reported‡	100.0	0	0	0	0	0	0	1.2	1.1	0.1	0	98.8
TOTAL	100.0	54.4	47.0	7.5	5.3	4.3	1.0	2.6	2.1	0.5	12.2	25.4

---

*Includes part-time specialists.
†Includes unlisted specialties as well as sub-specialties of those listed.
‡Includes primarily Interns and Residents.

Note: Per cents read horizontally.

mation relate to practicing physicians only. The data contain, however, information about physicians employed by the Federal government, a group which is often excluded from California physician statistics because of technical difficulties.

It should be noted that this overall total represents a net gain of approximately 1,961 physicians since April 1963, or a net annual increase of approximately 700. This increase, incidentally, was not quite sufficient to have maintained the statewide physician/population ratio of 181/100,000 which existed in 1963. The ratio as of 1965 was 180/100,000.

The largest single medical specialty, by a substantial margin, continues to be General Practice. Over one physician in four (26.3 per cent) is a General Practitioner. This category includes those who have indicated a part-time specialty as well as those in full-time General Practice only. In 1963 the proportion of G.P.'s was 29.6 per cent. The next most prevalent specialties are Internal Medicine (13.5 per cent), General Surgery (8.4 per cent) and Psychiatry (6.8 per cent). Table 1a contains breakdowns of numbers of physicians by specialty and by their source of professional income.

Table 1b presents information as to proportions of physicians in each of twelve medical specialties whose professional income is derived from various sources. There are five major categories of professional income: 1. Group Practice (income-sharing basis), 2. Fee-for-service (only), 3. Fee-for-Service with Part-time Salary, 4. Full-time Salary with some Fee-for-Service, and 5. Full-time Salary (only). Additionally, all physicians with any Fee-for-Service aspect of their practice are further categorized according to "individual practice" and "partnership or group (not an income-sharing basis)."

Among all physicians, well over half (54.4 per cent) indicated that their incomes are entirely from Fees-for-Service. Most of these (47.0 per cent) are in individual practice, with the remainder (7.5 per cent) in either partnerships or groups.

The next largest block of practicing physicians is comprised of those who practice on full-time salaries only. This group constitutes over one physician in four (25.4 per cent) and includes interns, residents, full-time hospital staff physicians, and federal government employees, among others. Almost one physician in eight (12.2 per cent) is in group practice, and the remainder combine Fees-for-Service with a salaried practice. Among this latter group, more than two out of three are primarily on a Fee-for-Service basis; the remaining third are on full-time salary, but receive some Fees-for-Service in addition.

There is considerable variation in source of income among the separately listed medical specialties. Over three out of four G.P.'s (76.8 per cent) are on a Fee-for-Service only basis, whereas fewer than two out of five Psychiatrists (39.5 per cent) and Radiologists (35.5 per cent) and one out of four Pathologists (23.7 per cent) list Fees-for-Service as their only source of income. Among M.D.'s in Fee-for-Service only, those in individual practice are prevalent in all specialties; among some (e.g., Pediatrics, Pathology, Radiology, Orthopedics), however, partnerships and groups are considerably more common than among others.

Proportions of physicians in group practice, regardless of medical specialty, generally cluster closely around the overall average of 12.2 per cent. Radiology and Orthopedics exceed the average by a wide margin, however, with 25.2 and 20.1 per cent, respectively, in Group Practice. Only 2.0 per cent of Psychiatrists are in Group Practice.

Of the total 25.4 per cent of physicians on full-time salaries, without any Fee-for-Service income, a high proportion are those with "no specialty reported." This group comprises primarily interns and residents. Among the specialties with high proportions of physicians on full-time salaries are Pathology (50.4 per cent) and Psychiatry (38.7 per cent). It should be noted that a very small proportion of General Practitioners (7.0 per cent) are on full-time salaries only.

Table 2 indicates numbers and per cents of physicians by medical specialty according to their principal employer. Among all physicians, two out of three (66.6 per cent) are self-employed and the remaining third employed by others. Of the latter group, 7.7 per cent of the total work for an agency of the Federal government and the remaining 25.7 per cent for other types of agencies. More than half of all non-Federal employees work in hospitals, with another 5.5 per cent employed by a clinic or another physician. Among those M.D.'s in the employ of the Federal Government, more than half are in the armed forces, another sizable group is employed by the Veterans' Administration, and a smaller group by the U.S. Public Health Service.

TABLE 2.—*Number and Per Cent of Practicing Physicians in California: Principal Employer by Medical Specialty, August 1965*

			Physicians Employed by Other Persons or Agencies																									
																	Federal Government Employees											
	Self-Employed		*Total Employed Non-Federal*		*Research Institution*		*Clinic or Physician*		*Educational Institution*		*Non-Federal Public Health Depts.*		*Non-Federal Hospitals*		*Industry or Pharmaceutical Co.*		*Total*		*Armed Forces*		*USPHS*		*V. A.*		*Other*	
Medical Specialty	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No*	*Per Cent*	*No.*	*Per Cent*
Gen. Practice* ..	7,276	34.6	708	8.7	2	2.4	398	23.1	41	3.8	19	4.3	234	5.1	14	6.7	315	13.0	264	18.8	16	10.1	31	3.8	4	9.9
Anesthesiology ..	969	4.6	235	2.9	2	2.4	38	2.2	41	3.8	1	0.2	153	3.4	0	0	53	2.2	33	2.3	1	0.6	19	2.3	0	0
Gen. Surgery	1,818	8.7	612	7.5	2	2.4	136	7.9	53	4.9	7	1.6	412	9.0	2	1.0	212	8.7	132	9.3	16	10.1	63	7.7	1	2.4
Internal Med.	2,667	12.7	1,154	14.3	13	15.9	324	18.8	190	17.4	16	3.6	591	13.0	20	9.6	451	18.5	184	13.0	39	24.6	225	27.5	3	7.3
Ob.-Gyn.	1,365	6.5	384	4.7	2	2.4	112	6.5	42	3.8	6	1.4	222	4.9	0	0	89	3.7	84	5.9	0	0	3	0.4	2	4.9
Ophthalmology ..	781	3.7	154	1.9	2	2.4	49	2.8	19	1.7	1	0.2	83	1.8	0	0	49	2.0	33	2.3	4	2.5	12	1.5	0	0
Ortho. Surgery ..	739	3.5	231	2.8	1	1.2	78	4.5	20	1.8	0	0	129	2.8	3	1.4	80	3.3	54	3.8	4	2.5	22	2.7	0	0
Otolaryngology ..	468	2.2	97	1.2	0	0	38	2.2	11	1.0	3	0.7	44	1.0	1	0.5	43	1.8	26	1.8	0	0	17	2.1	0	0
Pathology	276	1.3	432	5.3	9	11.0	67	3.9	70	6.4	6	1.4	278	6.1	2	1.0	95	3.9	37	2.6	5	3.1	50	6.1	3	7.3
Pediatrics	1,032	4.9	568	7.0	8	9.8	128	7.4	109	10.0	52	11.8	265	5.8	6	2.9	77	3.2	66	4.7	8	5.0	1	0.1	2	4.9
Psychiatry	1,107	5.3	822	10.1	6	7.3	68	3.9	80	7.3	38	8.6	629	13.8	1	0.5	221	9.1	80	5.7	11	6.9	128	15.7	2	4.9
Radiology	664	3.2	382	4.7	2	2.4	116	6.7	62	5.7	1	0.2	199	4.4	2	1.0	111	4.6	60	4.2	4	2.5	47	5.8	0	0
Others with Specialties†	1,849	8.8	1,421	17.6	24	29.4	175	10.1	284	26.0	276	62.6	515	11.3	147	70.6	475	19.4	231	16.3	31	19.5	189	23.1	24	58.6
No Specialty Reported‡	0	0	908	11.3	9	11.0	0	0	70	6.4	15	3.4	804	17.6	10	4.8	161	6.6	131	9.3	20	12.6	10	1.2	0	0
TOTAL	21,011	100.0	8,108	100.0	82	100.0	1,727	100.0	1,092	100.0	441	100.0	4,558	100.0	208	100.0	2,432	100.0	1,415	100.0	159	100.0	817	100.0	41	100.0
Per Cent Breakdown of All Physicians by Principal Employer	66.6		25.7		0.3		5.5		3.5		1.4		14.3		0.7		7.7		4.5		0.5		2.6		0.1	

---

*Includes part-time specialists.

†Includes unlisted specialties as well as sub-specialties of those listed.

‡Includes primarily Interns and Residents.

Among self-employed physicians in California, there are more General Practitioners than the combined total of the next four most populous specialties. Over one out of three self-employed physicians (34.6 per cent) is in General Practice, while the comparable proportion among *all* physicians is considerably closer to one in four. The next highest groups within the self-employed category are Internists (12.7 per cent). General Surgeons (8.7 per cent), Obstetrician-Gynecologists (6.5 per cent) and Psychiatrists (5.3 per cent).

Among all physicians employed outside the Federal government, the greatest proportions are in Internal Medicine (14.3 per cent) and Psychiatry (10.1 per cent). Relatively few (8.7 per cent) are in General Practice. Most (17.6 per cent) are in such specialties as Public Health, Administrative Medicine, Occupational Medicine, and Preventive Medicine, and are, therefore, included in the aggregate "Other Specialty" category. Many others (11.3 per cent) are in Internships and are, therefore, counted in the "No Specialty Reported" category.

Physicians employed by the Federal government come from varied medical specialties, with the highest proportion from the ranks of the Internists. A relatively low, although still substantial percentage, are in General Practice. High proportions come from such numerically minor medical specialties as Aviation Medicine, Administrative Medicine, Neurology, and Pulmonary Diseases. Most of the 24 physicians who work for Federal agencies termed "other" are in Administrative Medicine.

County Teaching Hospitals

A Statement of the Council of the California Medical Association

On 7 May 1966 the council of the California Medical Association issued a supplemental statement to a previous policy position (16 January 1966) pertaining to medical staff structure and financial payment in county/teaching hospitals, resulting from recently enacted legislation (California Medical Assistance Program and the federal medicare law). The combined statements appear below:

Statement Approved by the Council, 7 May 1966:

The California Medical Association has observed with great interest the developments, and the impact on physician staff relationships, of payments from CAL-MAP resources for care of patients in county hospitals and medical teaching hospitals.

There is growing concern that certain limiting patterns of physician staff organization and payment, now developing in some sections of the state, may continue or accentuate the separation of certain CAL-MAP patients in public and teaching facilities.

Recognizing that multiple avenues of adaptation are being considered, CMA urges that all interested parties now undertake a careful and thoughtful re-evaluation of the objectives and issues, before the limiting patterns which now seem to be evolving become prematurely established in an inflexible mold.

Statement Approved by the Council, 16 January 1966:

1. Federal Public Law 89-97 and California Assembly Bill 5 establish need for a new patient-physician-hospital relationship in California's county hospitals.

2. Effective 1 March 1966, many welfare recipients and medical indigents covered by Assembly Bill 5 will begin to receive their medical care in a new way. They will have eligibility identification cards which will permit them to receive medical and hospital service in physicians' private offices and in all qualified community hospitals. Many of these recipients of public medical care will become part of the community's medical mainstream rather than being segregated in county hospitals.

3. As part of this intermingling of patients, Assembly Bill 5 authorizes county hospitals to provide general community service by permitting them to admit paying patients.

Section 14000.2 provides:

> "During the time this chapter is effective and notwithstanding other provisions of the Welfare and Institutions Code and Health and Safety Code, the board of supervisors of each county may prescribe rules which authorize the county hospital to integrate its services with those of other hospitals into a system of community

service which offers free choice of hospitals to those requiring hospital care. The intent of this section is to eliminate discrimination or segregation based on economic disability so that the county hospital and other hospitals in the community share in providing services to paying patients and to those who qualify for care in public medical care programs. In prescribing rules under which the county hospital may provide community hospital services described in this section, the board of supervisors shall provide a basis under which patients may be attended by their own personal physicians who are professionally qualified for staff membership in the county hospital."

4. Because county hospitals represent a large capital investment which should be used and because they have needed capacity to serve the people of California, they should be encouraged to operate as authorized by section 14000.2.

5. In operating as community hospitals to serve the general public, county hospitals should modify the traditional basis of depending for medical service on volunteer, salaried, resident physician and intern staffs.

6. Modification of the present basis creates many organizational and staffing questions, in patient-physician-hospital relationships.

7. A reasonable approach to these questions is to establish the goal that county hospitals organize themselves from a medical staffing standpoint as would comparable non-county hospitals. Thus, the non-teaching county hospital should be organized like its non-county counterpart. Similarly the teaching and medical school affiliated county hospitals should be organized like their non-county counterparts.

8. In all county hospitals it is imperative that medical care be of high quality. In teaching and medical school affiliated county hospitals strenuous effort should also be made to gain the highest quality and quantity of education for doctors and other professions in the health field. It is obvious there will be continuing heavy demands on doctors, other personnel and all other health resources as a result of constantly growing scientific achievement with corresponding public expectation and demand for more and better service.

Large urban county hospitals have traditionally played an important role in collaboration with medical schools in the clinical education of undergraduate medical students. This teaching role must be preserved and strengthened and the implementation of the new legislation must preserve this role.

Many county hospitals and particularly large urban county hospitals have high quality internship and residency training programs. These training programs provide well trained physicians for California. The implementation of the new legislation must preserve this house staff teaching role.

9. By establishing a basis whereby the recipient of public medical care is intermingled with the general population, Public Law 89-97 and Assembly Bill 5 create a system under which medical fees will become available to provide compensation for these services.

10. Public Law 89-97 and Assembly Bill 5 distinguish between medical and institutional services. Under these programs medical fees should not be diverted to hospitals, nor hospital charges used to compensate doctors for medical services.

11. County hospitals should provide a basis for qualified physicians in the community to have staff privileges with the usual physician compensation on a fee basis, as exists in other comparable community hospitals.

12. In county hospitals with intern and resident physician programs there also is need for full-time salaried medical staffing. When the hospital is affiliated with a medical school, full-time salaried staffing also includes university faculty. When full-time medical staff and faculty provide patient services, fees should be collected for their services.

13. When county hospitals with medical school affiliation operate on a community hospital basis with paying patients, medical services which patients receive will involve:

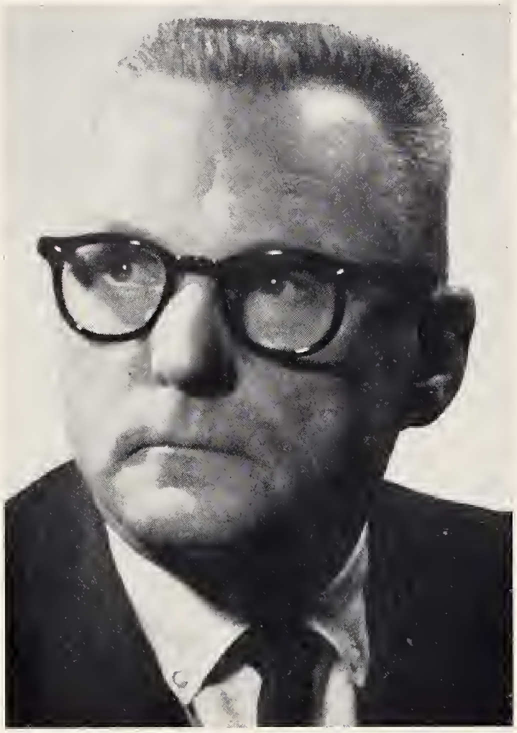
a. Physicians in private practice
b. Full-time hospital staff
c. Faculty
d. Resident physicians and interns.

14. In county hospitals with programs for the education of resident physicians and interns, a basis should be established for collecting medical fees and their appropriate control and distribution by physicians.

NEWS & NOTES

NATIONAL • STATE • COUNTY

New Dean at U. C. School of Medicine, San Francisco



STUART C. CULLEN, M.D.

Dr. Stuart C. Cullen, who was appointed dean of the University of California School of Medicine, San Francisco, had served as Associate Dean since 1963 and had been a member of the faculty for eight years. The new dean received his B.S. and M.D. degrees at the University of Wisconsin. From 1938-1958 he was on the faculty of the State University of Iowa, where he became professor of surgery and anesthesiology and chairman of the division of anesthesiology. In 1958, Dr. Cullen joined the U. C. Medical Center as professor of anesthesia, clinical professor of pharmacology and experimental therapeutics and chairman of the Department of Anesthesia. In that same year he received the *Modern Medicine* Distinguished Achievement Award and in 1964 he was presented the Distinguished Service Award of the American Society of Anesthesiologists, an organization of which he is a past president.

Dr. Cullen has been on several World Health Organization committees and was instrumental in organizing the Anesthesiology Training Center established in Copenhagen in 1950. His services as consultant to local and national groups includes: The National Research Council, U.S. Naval Hospital, Oakland, Napa State Hospital, and the National Institutes of Health, Bethesda, Maryland. Currently he is a member of the National Institutes of Health Surgery Study Section.

LOS ANGELES

Dr. J. Edward Berk, professor and chairman of the Department of Medicine, of the University of California, California College of Medicine, Los Angeles, is the recipient of the 1966 **Rudolf Schindler Award** of the American Society for Gastrointestinal Endoscopy.

The award was given in recognition of Dr. Berk's innovations in diagnostic instrumentation and his contributions to the diagnosis of gastrointestinal disorders.

RIVERSIDE

The 14th annual meeting of the **Pacific Coast Fertility Society** will be held at El Mirador Hotel, Palm Springs, California, 13 to 16 October 1966. Among the guest lecturers are Dr. S. J. Behrman, professor of obstetrics and gynecology, University of Michigan; Dr. Nicholas Vorys, of the Department of Obstetrics and Gynecology, Ohio State University; and Dr. Vagn Sele and Dr. V. Aasted Frandsen, both of Copenhagen.

Further information may be obtained by writing to the office of the Society at 5410 Wilshire Boulevard, Los Angeles.

SAN FRANCISCO

The Regents of the University of California have appointed **Willard C. Fleming,** D.D.S., as Chancellor of the University of California Medical Center in San Francisco for 1966-67. Dr. Fleming, formerly Vice Chancellor, succeeds John B. deC. M. Saunders, M.D., who is returning to teaching and research.

The Regents also made **three other major administrative appointments** at the Medical Center, all effective 1 July.

Stuart C. Cullen, M.D., who was Associate Dean of the School of Medicine, has been made Dean; Harold A. Harper, Ph.D., formerly Dean of the Graduate Division, became Vice Chancellor Graduate Studies and Research; and Leslie L. Bennett, M.D., formerly Acting Vice Chancellor for Academic Affairs, has been named Vice Chancellor for that function.

* * *

Dr. Robert C. Combs, San Francisco, has been named president of the State Board of Medical Examiners to succeed Dr. Nicholas V. Oddo, Long Beach, who died suddenly 10 June while in San Francisco to attend a regular meeting of the Board.

Dr. Combs has been a member of the Board since 1964.

SANTA CLARA

Dr. Keith B. Taylor has been named the George de Forest Barnett Professor of Medicine at Stanford University School of Medicine. Dr. Taylor is currently an associate professor of medicine and head of the Division of Gastrointestinal Medicine. He also is chief of gastrointestinal medicine of the Stanford medical staff at the Palo Alto-Stanford Hospital Center.

The George de Forest Barnett Professorship honors a physician famed for his interest in both patients and students as human beings. The man for whom it was named was chief of the Stanford Medical Service at the San Francisco City and County Hospital for 25 years.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information contact: W. F. Norwood, Ph.D., Associate Dean, Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information contact. Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information contact: Donald Brayton, M.D., Assistant Dean for Postgraduate Medical Education, 15-39 Rehabilitation Center, University of California Center for Health Sciences, Los Angeles 90024, 478-9711, Ext. 4345.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

JULY

July 10-12—**Hospital Infections Control.** Neuropsychiatric Institute Auditorium, 720 Westwood Plaza Bldg., No. C-18-183, West Los Angeles. Sunday-Tuesday. Contact: John W. Brown, M.D., Bureau of Communicable Diseases, Department of Public Health, 2151 Berkeley Way, Berkeley 94704.

July 30-August 10—**Annual Postgraduate Refresher Course in Honolulu and Kauai.** USC. Saturday-Wednesday. 43½ hours. $125.

AUGUST

August 7-10—**Advanced Seminars in Pediatrics.** "Immunologic Principles and Their Clinical Applications." UCLA at Lake Arrowhead. Sunday-Wednesday. 15 hours. $110.

August 12-13—**National Conference on Infant Mortality.** Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Harold S. Morgan, M.D., chairman, Committee on Maternal and Child Care, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

August 13-14—**Obstetrics and Gynecology.** UCLA. Saturday-Sunday. 16 hours.

August 17-21—**Advanced Seminars in Dermatology.** UCLA at Lake Arrowhead. Wednesday-Sunday. 15 hours.

August 21-24—**Advanced Seminars in Internal Medicine.** UCLA at Lake Arrowhead. Sunday-Wednesday. 15 hours. $110.

August 27—**American Institute of Ultrasonics in Medicine.** Sheraton-Palace Hotel, San Francisco. Saturday. Contact: John H. Aldes, M.D., executive director, 4833 Fountain Avenue, Los Angeles 90029.

August 28—**American Association of Electromyography and Electrodiagnosis.** Sheraton-Palace Hotel, San Francisco. Sunday. Contact: Max Karl Newman, M.D., director, 16861 Wyoming Avenue, Detroit 48221.

August 28-31—**Medicine and Religion.** UCLA at Lake Arrowhead. Sunday-Wednesday. 15 hours.

August 28-September 2—**American Academy of Physical Medicine and Rehabilitation.** Sheraton-Palace Hotel, San Francisco. Sunday-Friday. Contact: Harriet E. Gillette, M.D., secretary, Cleveland Clinic, Cleveland.

SEPTEMBER

September 8-10—**Saint John's Hospital Annual Postgraduate Assembly.** SJH, 1328 22nd Street, Santa Monica. Thursday-Saturday. Contact: John C. Eagan, M.D., director, SJH.

September 10-11—**Health of the School Child.** UCSF. Saturday-Sunday.

September 13-November 29—**Emergency Management of the Acutely Ill Patient.** USC at Los Angeles County Hospital. Tuesday evenings. 18 hours. $80.

September 14-16—**Hospital Infections Control.** Auditorium, Medical Sciences Bldg., UCSF. Wednesday-Friday. Contact: John W. Brown, M.D., Bureau of Communicable Diseases, Department of Public Health, 2151 Berkeley Way, Berkeley 94704.

September 14-December 21—**Psychotherapeutic Principles and Practice for Non-Psychiatrists.** UCSF. Wednesdays.

September 15-16—**Merritt Hospital Medical Seminar.** Claremont Hotel, Berkeley. Thursday-Friday. 10 hours. Contact: Robert R. Crosbie, M.D., secretary of the Staff, MH, Hawthorne and Webster, Oakland.

September 16-17—**Advances in Electrovectocardiography.** Sponsored by Daniel Freeman Hospital, 333 N. Prairie Ave., Inglewood. To be held at the Statler Hotel and Los Angeles County Medical Association Bldg., Los Angeles. Friday-Saturday. 10 hours. $15 members, $25 non-members. Contact: W. Graf, M.D., chairman, 3701 Stocker Street, Los Angeles 90008.

September 16-18—**New Concepts in the Management of Common Ailments of the Human Foot.** UCSF. Friday-Sunday.

September 17—**Annual Symposium on Cardiovascular Disease.** Sponsored by the Heart Associations of Ventura and Santa Barbara Counties. Biltmore Hotel, Santa Barbara. Saturday. 6 hours. $12.50. Contact: Sara Clyde, executive director, 18 La Arcada Court, Santa Barbara.

September 17-18—**Group Psychotherapy.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

September 19-May 22—**Radiological Physics.** UCSF. Monday evenings.

September 19-October 12—**Sacramento Valley Circuit Courses.** CMA in cooperation with Stanford. Dunsmuir: Mondays; Chico: Tuesdays; Auburn: Wednesdays. $30. Spring and Fall. Spring Courses: February 20-March 15.

September 20-October 25—**Specific Syndromes Associated with Mental Retardation.** UCSF at Sonoma State Hospital, Eldridge. Tuesdays.

September 20-December 6—**Medical Radio Conferences.** UCSF. Tuesdays.

September 21-23—**Recent Advances in Internal Medicine.** UCSF. Wednesday-Friday.

September 22-24—**Surgical Pathology of the Eye.** UCSF. Thursday-Saturday.

September 22-December 15—**Bedside Clinics and Set Clinics in Internal Medicine.** USC. Thursday evenings. 24 hours. $80.

September 23—**Annual Symposium of the Northern California Chapter, National Kidney Foundation.** UCSF. Friday.

September 24-25—**Child Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

September 26—**Society for Pediatric Radiology.** Hilton Hotel, San Francisco. Monday. Contact: John L. Gwinn, M.D., treasurer, Children's Hospital, 4614 Sunset Blvd., Los Angeles 90027.

September 26-October 7—**Intensive Review of Internal Medicine.** USC at Los Angeles County General Hospital. Mornings daily for 2 weeks. 40 hours. $80.

September 27-30 — **American Roentgen Ray Society.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: C. Allen Good, M.D., executive secretary, Mayo Clinic, 200 First Street, SW, Rochester, Minn. 55901.

September 28-29 — **Annual Brennemann Lectures.** "Newborn Problems, Infectious Disease and Clinical Immunology." Presented by Los Angeles Pediatric Society. Ambassador Hotel, Los Angeles. Wednesday-Thursday. $35. Contact: Paul F. Wehrle, M.D., president, LAPS, 9209 Sixth Avenue, Inglewood 90305.

September 28-29—**Los Angeles County Heart Association Annual Symposium on Heart Disease.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Professional Symposium Committee, 2405 West Eighth Street, Los Angeles 90057.

September 28-30—**Annual Postgraduate Symposium on Heart Disease.** Sponsored by San Francisco Heart Association. St. Francis Hotel, San Francisco. Wednesday-Friday. 18 hours. $35. Contact: Gene C. Taylor, executive director, SFHA, 259 Geary Street, San Francisco.

September 28-30—**American Association of Medical Clinics.** Hotel Del Coronado, San Diego. Wednesday-Friday. Contact: Edwin P. Jordan, M.D., executive director, P.O. Box 58, Charlottesville, Va. 22902.

September 30-October 1—**Annual Professional Symposium on Heart Disease.** Town and Country Hotel, San Diego. Friday-Saturday. 12 hours. $5. Contact: James E. Lasry, M.D., chairman, San Diego County Heart Association, 3545 Fourth Avenue, San Diego 92103.

OCTOBER

October 1—**Shufelt Society of Santa Clara County Fall Seminar.** Obstetrics and Gynecology. Auditorium, Santa Clara County Administration Bldg., 70 West Hedding Street, San Jose. $15. Contact: H. W. Christopher, M.D., secretary, 621 E. Campbell Avenue, Campbell.

October 4-November 15—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

October 4-November 29—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Wednesdays.

October 6-8—**Newer Aspects of Obstetrics and Gynecology.** UCSF. Thursday-Saturday.

October 6-8—**American Association for Surgery of Trauma.** Santa Barbara Biltmore Hotel, Santa Barbara. Thursday-Saturday. Contact: Sawnie R. Gaston, M.D., secretary, 180 Ft. Washington Avenue, New York 10032.

October 8-9—**Recent Developments in Nuclear Medicine.** UCLA. Saturday-Sunday. 16 hours.

October 8-9—**Stroke.** UCSF at St. Mary's Hospital, San Francisco. Saturday-Sunday.

October 10-14—**American College of Surgeons.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John P. North, M.D., director, 55 Erie Street, Chicago 60611.

October 10-14—**Pediatric Allergy.** UCSF. Monday-Friday.

October 11—**Northeastern California Chapter of the Arthritis Foundation Symposium.** Mercy Hospital, Sacramento. Tuesday. Contact: Harold B. Strauch, M.D., 4101 J Street, Sacramento 95819.

October 13-14—**Current Concepts in Obstetrics and Gynecology.** USC. Thursday-Friday. 14 hours.

October 14-15—**Western Industrial Medical Association.** International Hotel, Los Angeles. Friday-Saturday. Contact: Ellsworth F. Marriner, M.D., secretary, Autonetics Division, North American Aviation, Inc., 3370 Miraloma Road, Anaheim 92803.

October 14-16—**California Society of Internal Medicine Annual Meeting.** Sahara-Tahoe Hotel, Lake Tahoe. Friday-Sunday. $10.: non-members of CSIN and/or ASIN. Contact: Mrs. Nancy V. Louw, executive secretary, CSIN, 350 Post Street, San Francisco.

October 15-16—**Alcoholism.** UCSF. Saturday-Sunday.

October 16-20—**American Orthotics and Prosthetics Association.** Riviera Hotel, Palm Springs. Sunday-Thursday. Contact: Lester A. Smith, executive secretary, 919 18th St., NW, Suite 130, Washington, D.C.

October 18-November 29—**Communications in Psychiatry.** UCSF at Agnews State Hospital, San Jose. Tuesdays. 12 hours.

October 19—**Newborn Infant Care.** USC at Los Angeles County General Hospital. Wednesday. 8 hours. $25.

October 21-22—**Calcium.** UCSF. Friday-Saturday.

October 21-22—**Mental Health and the Aging Process.** UCSF. Friday-Saturday.

October 21-25—**Association of American Medical Colleges.** San Francisco Hilton Hotel, San Francisco. Friday-Tuesday. Contact: Robert C. Berson, M.D., executive director, 1501 New Hampshire Avenue, NW, Washington, D.C. 20036.

October 22-23—**Family Therapy.** UCSF at Modesto State Hospital, Modesto. Saturday-Sunday.

October 24-28—**Spinal Cord Injuries.** UCSF at Kaiser Foundation Rehabilitation Center, Vallejo. Monday-Friday.

October 27-November 1—**Pacific Dermatologic Association.** El Mirador Hotel, Palm Springs. Thursday-Tuesday. Contact: Mortimer S. Falk, M.D., secretary-treasurer, 503 S. Arlington, Reno, Nevada.

October 27-November 3—**American School Health Association.** Jack Tar Hotel, San Francisco. Thursday-Thursday. Contact: A. O. DeWeese, M.D., executive secretary, 515 E. Main Street, Kent, Ohio 44240.

October 28—**Kern County General Hospital Postgraduate Conference (and Alumni Day).** KCGH, 1830 Flower Street, Bakersfield. Friday. 8 hours. Contact: George A. Paulsen, M.D., KCGH.

October 29 — **The Medical Management of Unwed Mothers.** St. Anne's Maternity Hospital, 155 North Occidental Blvd., Los Angeles 90026. Saturday. 9:00 a.m. to 4:00 p.m. $25. Contact: Clyde V. Von Der Ahe, M.D., president, Medical Staff, SAMH.

October 29-30 — **Current Management of Tumors.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.

October 30-November 2—**California Academy of General Practice Annual Scientific Assembly.** El Cortez Convention Center, San Diego. Sunday-Wednesday. 13 hours. $10.: non-members. Contact: William W. Rogers, executive secretary, CAGP, 9 First Street, San Francisco.

October 31-November 4—**American Public Health Association.** Civic Auditorium, San Francisco. Monday-Friday. Contact: Berwyn F. Mattison, M.D., executive director, 1790 Broadway, New York 10019.

October 31-November 4—**American Association of Public Health Physicians.** San Francisco. Monday-Friday. Contact: John S. Neill, M.D., secretary, P.O. Box 1731, Tampa, Florida 33601.

NOVEMBER

November 2-3—**American College of Preventive Medicine.** San Francisco Hilton, San Francisco. Wednesday-Thursday. Contact: Robert E. Coker, Jr., M.D., executive secretary, P.O. Box 1263, Chapel Hill, North Carolina 27514.

November 4-6—**Executive Health.** UCSF. Friday-Sunday.

November 5-6—**Somatic Mask of Psychiatric Illness.** USCF at Fresno Community Hospital, Fresno. Saturday-Sunday.

November 5-6—**Gastro-Intestinal Diseases.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

November 9—**Annual Science Lecture of the Southern California Region, American College of Physicians.** "Current Problems of Oceanography." Wednesday. 7:30 p.m. $10. Contact: W. Philip Corr, M.D., governor, SCACP, 3660 Arlington Avenue, Riverside 92506.

November 9-10—**Workshop in Cardiac Arrhythmias.** USC. Wednesday-Thursday. 16 hours.

November 11—**Medicine in Surgery Symposium.** Sponsored by Fresno-Madera-Kings Counties Medical Societies. Del Webb Center, Fresno. Friday. 6 hours. Contact: Cam Covington, M.D., 2057 High Street, Selma.

November 12-13—**Annual Clinical Cancer Conference.** UCSF. Saturday-Sunday.

November 18-19—**Annual Staff Seminar: "Cancer of the Abdomen."** California Hospital, 1414 South Hope Street, Los Angeles. Friday-Saturday. 10½ hours. $15. Contact: K. L. Senter, M.D., CH.

November 18-19—**Orthopedics.** UCSF. Friday-Saturday.

November 28—**Medical Aspects of Well Being—Rehabilitation.** UCSF. Monday.

November 30-December 3—**Viral Diseases of the Eye.** UCSF. Wednesday-Saturday.

DECEMBER

December 3—**Symposium on Shock.** Presented by Permanente Medical Group, 2200 O'Farrell Street, San Francisco. Sheraton-Palace Hotel, San Francisco. Saturday. Contact: L. E. Harris, M.D., Co-Chief, Department of Medicine, PMG.

December 3-4—**Medical Practice and the Law.** UCLA. Saturday-Sunday.

December 10-11—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

December 10-11—**An Eclectic Approach to Psychiatry.** UCSF at Mendocino State Hospital. Saturday-Sunday.

Courses Offered Continuously or by Arrangement

USC:

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Fifty-two issues $100. Physicians may register at any time.

Advanced Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Fifty-two issues $85. Physicians may register at any time.

LLU:

Continuously—**Illustrated Medical Lectures.** One to three lectures monthly, by yearly subscription. Tape recorded 30 minute lectures with synchronized 35 mm. filmstrips. Designed as a postgraduate refresher and to upgrade educational opportunity.

Audio-Digest Foundation

Audio-Digest Foundation (a non-profit subsidiary of the California Medical Association) provides by subscription twice-a-month tape-recorded summaries of leading national meetings and authoritative surveys of current literature. Seven separate services in: General Practice, Surgery, Internal Medicine, Obstetrics-Gynecology, Pediatrics, Anesthesiology, and Ophthalmology. A new Catalog of outstanding lectures and panel discussions in all areas of medical practice is also available. For information, write: Mr. Claron L. Oakley, Editor, 619 South Westlake Avenue, Los Angeles.

TO HAVE YOUR MEETING OR PROGRAM LISTED IN CALIFORNIA MEDICINE

FILL OUT AND MAIL THIS BLANK TO THE ADDRESS GIVEN

(COPY MUST BE **RECEIVED** NOT LATER THAN THE **FIFTH OF THE MONTH PRECEDING** ISSUE)

Continuing Medical Education, California Medical Association
693 Sutter Street, San Francisco, California 94102

Name of Organization____________________

Meeting or Program____________________

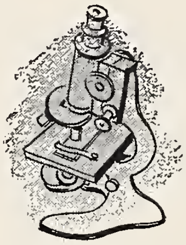
____

Date____________________Time__________

Place____________________Fee, If Any__________

Contact for Information:____________________
(give name, title, address)

____



FOR A CLEAN START IN VAGINITIS THERAPY

superior cleansing action ■ STOMASEPTINE is "a highly effective mucolytic cleansing agent"[1] that removes debris and flushes out secretions more thoroughly than acid douches.[1] Alkaline STOMASEPTINE "dissolves and removes leukorrheal secretions"[1]—whereas acid douches tend to "coagulate or set the vaginal contents."[2] Low surface tension and release of nascent oxygen contribute to deep penetration and cleansing of rugae.

enhances specific therapy ■ Thorough cleansing of the vaginal vault with STOMASEPTINE enhances the effectiveness of specific vaginitis therapy, ensures maximum contact of topical medication with mucosa.

excellent patient acceptance ■ Anti-pruritic and soothing, pleasantly scented—patients feel "fresh and clean."

1. Weese, H.: Personal Communication, Sept. 25, 1964. 2. Glynn, R.: Obst. & Gynec. 20:369, 1962.

Contains: sodium perborate, sodium bicarbonate,
sodium chloride, sodium borate, menthol, thymol,
eucalyptol, methyl salicylate and aromatics—
6 oz. and 15 oz. jars; cartons of 12 10-gm. packets

Literature and professional supply on request.

HARCLIFFE LABORATORIES, INC. BROOKLYN, New York 11217

STOMASEPTINE®
DOUCHE POWDER

AMA Takes Responsibility For Project Vietnam

The American Medical Association is taking complete responsibility for Project Vietnam, the program under which American physicians volunteer to provide medical care to South Vietnamese civilians. Under AMA auspices the program will be known as AMA Volunteers for Vietnam.

The AMA has signed a contract with the State Department's Agency for International Development (USAID), assuming complete responsibility for recruitment and the administration of the program.

The announcement was made by Percy E. Hopkins, M.D., chairman of the AMA Board of Trustees, and reported in the May 30 issue of *The AMA News.*

USAID has asked the AMA to become more strongly involved in the program. The AMA had previously helped recruit physicians but administration was handled for USAID by the People-to-People Foundation, Inc.

Under the program, U.S. physicians volunteer to work in South Vietnamese civilian hospitals on a short-term basis, usually 60 days.

A newly appointed AMA Volunteers for Vietnam field director, Malcolm Phelps, M.D., El Reno, Okla., will be stationed in Saigon beginning July 1, Dr. Hopkins said.

Dr. Phelps, a member of the AMA House of Delegates, will maintain liaison between volunteers and USAID, visit the 16 provincial hospitals where volunteers are stationed, and provide orientation for newly arrived volunteers.

Dr. Hopkins said he hopes the AMA will be able to recruit more specialists for the program. Especially needed in South Vietnam are orthopedic and plastic surgeons, radiologists, and chest physicians, in addition to a continuing need for internists and general practitioners.

The possibility of recruiting with the aid of medical schools and medical societies is being explored.

Up to 32 physicians are needed every 60 days to fulfill the need.

The physician recruitment program was created in response to a request from the South Vietnamese government to the U.S. government for help in bringing volunteer American physicians to South Vietnam. Of the approximately one thousand doctors in South Vietnam, about 700 are in military service, leaving only about 300 to care for 16 million civilians.

Physicians interested in the program may write to AMA Volunteers for Vietnam, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

For prompt, emphatic diuresis

aquaTAG®
(BENZTHIAZIDE)

NEW FROM TUTAG for prompt, comfortable diuretic action with a balanced excretion of sodium chloride and a lower potassium loss under normal dosage and diet regimen

DIURETIC ACTION: Clinically, the oral administration of AQUATAG (benzthiazide) results in diuretic activity within two hours with maximal natriuretic, chloruretic, and diuretic effects occurring during the fourth, fifth and sixth hours. Maintenance of response continues for approximately 12 to 18 hours. Acidosis is an unlikely complication since therapeutic doses of AQUATAG (benzthiazide) do not appreciably increase bicarbonate excretion. Edematous patients receiving 50 mg. of AQUATAG (benzthiazide) daily for five days developed a maximal increase in the rate of sodium excretion on the first day, and maintained this high rate until depletion of excessive body stores of sodium.

In congestive heart-failure patients, AQUATAG (benzthiazide) produced the same weight loss, during a 48-hour treatment period as did a maximally effective dose of hydrochlorothiazide.

DOSAGE: Diuresis, initially 50 to 200 mg.; maintenance 25 to 150 mg., daily. Hypertension 50 to 100 mg. initially, adjusted to 50 mg. t.i.d. or downward to minimal effective dosage level.

PRECAUTIONS AND SIDE EFFECTS: Electrolyte imbalance with hypokalemia, hypochloremic alkalosis and hyponatremia may occur. Other reactions may include blood dyscrasias, hyperuricemia and gout, nausea, jaundice, anorexia, vomiting, diarrhea, dizziness, paresthesia, photosensitivity and headache. Insulin requirements may be altered in diabetes.

WARNINGS: Dosage of coadministered antihypertensive agents should be reduced by at least 50%. Use with caution in edema due to renal disease; advanced hepatic disease or suspected presence of electrolyte imbalance. Stenosis or ulcer of small intestine have been reported with coated potassium formulas and should be administered only when indicated. Until further clinical experience is obtained, the use of the drug in pregnant patients should be carefully weighed against possible hazards to the fetus.

CONTRAINDICATIONS: AQUATAG (benzthiazide) is contraindicated in progressive renal disease or disfunction including increasing oliguria and azotemia. Continued administration of this drug is contraindicated in patients who show no response to its diuretic or antihypertensive properties.

Before prescribing or administering, read the package insert or file card available on request.

Available as 25 or 50 mg. scored tablets.

Request clinical samples and literature on your letterhead.

S. J. TUTAG
& COMPANY
Detroit, Michigan 48234

"Instant Air" t.i.d. keeps "air-hungry" patients trouble-free

Used regularly morning, noon and evening, Bronkometer gives patients sustained bronchodilator-decongestant action that makes breathing easier all day, every day. This convenient, easy-to-carry aerosol opens bronchioles and clears congestion . . . improves capacity for daily activity and so relieves anxiety . . . rarely hinders sleep thanks to its "remarkable freedom from cardiovascular or central nervous system stimulation."[1] Side actions are so low that of 373 patients studied, Bronkometer provided 87% excellent to good relief, with only 1.3% noting mild side effects.[1,2,3,4,5] In Bronkometer, Breon's exclusive bronchodilator, isoetharine,* is combined with thenyldiamine and the bronchovasoconstrictor phenylephrine for superior results.

*Dilabron®, brand of isoetharine

BRONKOMETER®

isoetharine 0.6%; phenylephrine 0.125%; thenyldiamine 0.05%

ASTHMA, CHRONIC BRONCHITIS, EMPHYSEMA

Superior because it contains isoetharine—Breon's exclusive bronchodilator

COMPOSITION: Bronkometer delivers at the mouthpiece 200 metered doses of: 350 mcg isoetharine methanesulfonate (0.6%); 70 mcg phenylephrine HCl (0.125%); and 30 mcg thenyldiamine HCl (0.05%) with saccharin, menthol and fluorochlorohydrocarbons as inert propellants. Preserved with ascorbic acid 0.1% and alcohol 30%.

RECOMMENDED DOSAGE: One or two inhalations with at least one minute between inhalations. Occasionally more may be required, however in most cases, inhalations need not be repeated more than every four hours. Dosage should be adjusted to the severity of the condition and response of the individual patient.

PRECAUTIONS: Bronkometer is unusually free from cardiovascular and other side effects, but the usual precautions associated with sympathomimetic amines should be observed. Bronkometer should not be administered simultaneously with epinephrine or similar compounds because of the possibility of tachycardia, although it may be alternated with these agents. Dosage must be carefully adjusted in patients with hyperthyroidism, hypertension, acute coronary disease, cardiac asthma, limited cardiac reserve and in individuals sensitive to sympathomimetic amines.

SUPPLIED: 10 ml pressurized aerosol vials complete with measured dose valve and oral nebulizer.

References: 1. Spielman, A. D.: *Curr. Therap. Res.* 3:235 (June) 1961. 2. Baker, A. G.: *Ann. Allergy* 22:180 (April) 1964. 3. Goldfarb, A. A. and Romanoff, A.: *Ann. Allergy* 20:307 (May) 1962. 4. Siegel, C.: *The Journal-Lancet* 82:461 (Nov.) 1962. 5. Taub, S. J.: *Clinical Medicine* (June) 1962.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y.

The discomforts of

DIARRHEA
MUCOUS COLITIS
DIVERTICULITIS
SPASTIC URETERITIS
BLADDER SPASM

are relieved by
direct musculotropic action
with.....

Trocinate®

BRAND THIPHENAMIL HCl

Available in 100 milligram pink sugar-coated tablets.

The high therapeutic index permits dosage sufficient to relieve spasm promptly. The usual initial dose is 4 tablets. Maintenance dosage is usually one or two tablets 4 times a day.

Trocinate *BRAND* THIPHENAMIL HCl
BETA-DIETHYLAMINOETHYL DIPHENYLTHIOACETATE HYDROCHLORIDE

Directly relaxes smooth muscle spasm
Combats hypermotility
Non-mydriatic, may be used in glaucoma

Trocinate (Thiphenamil HCl) has been found in three clinical studies, (J. Mo. Med. Assoc., 48:685-6; Med. Rec. & Annals, 43:1104-6; J. Urol., 73:487-93), to be effective and to be virtually free of side-effects. Fifteen years of wide clinical usage has affirmed the safety and effectiveness of Trocinate.

DISPENSED IN BOTTLES OF
100, 250 AND 2000 TABLETS
Literature and samples sent upon request

WM. P. POYTHRESS & CO., INC.
RICHMOND, VIRGINIA
Manufacturers of ethical pharmaceuticals since 1856

LSD Warning Still Applies

(Continued from Page 32)

foretold which person will suffer ill effects from the drugs; their effects seem to vary from time to time on an individual.

"Numbers of people promoting the hallucinogens are not aware of, and evidently do not care about, the harm caused by their use," Dr. Farnsworth said. "These persons typically pay little attention to precautions that any responsible investigator would demand."

Dr. Farnsworth listed statements of patients and witnesses that tell a great deal about the hazards of LSD:

"—I kept a journal while on the drugs. Later I read it and it was horrible. People were tearing each other apart. Also, I felt I was reading the worst pornography I had ever read."

"—Your mind seems to think about all the things it ordinarily doesn't want to think."

"—I had a compulsive urge to do violence to my children . . . nor do I know how great the gap was between the violent thoughts in my mind and their possible execution."

Said Dr. Farnsworth: "Those promoting the general use of these hallucinogens believe they 'expand consciousness' and give a man or woman new insights and new intellectual powers. Such testimony is common and makes it easy to understand the fascination these drugs exert on many people, especially on those of college age.

"On the claim that the hallucinogens 'free' the mind for creative work, it must be said that up to now we have had any amount of rhapsodic talk and writing, but no responsible proof. Meanwhile, the evidence accumulates steadily to indicate that the drugs do exert powerful and often damaging effect on the human system," Dr. Farnsworth said.

A new book by Dr. Farnsworth, *Psychiatry, Education, and Young Adults* is being published by Charles C Thomas Company. A chapter is devoted to LSD and other hallucinogenic drugs, in which these warnings are repeated.

The AMA's Council on Mental Health, of which Dr. Farnsworth is a member, urges all physicians to be on the alert in their communities for these drugs. The only legal source of supply of LSD, a drug manufacturing firm, recently ceased supplying medical researchers. Thus, any manufacture and use of LSD is now done without legal and medical authority.

"Until adequate controls are formulated," Dr. Farnsworth said "every physician has a duty to help prevent the unwise distribution of substances which are a real menace to mental and physical health.

autions and adverse reactions: The transitory drowsiness which
accur with hydroxyzine HCl usually disappears spontaneously
few days with continued therapy, or is correctable by dosage
ction. Dryness of the mouth may be seen with higher doses.
luntary motor activity, including rare instances of tremor and
ulsions, has been reported, usually on higher than recom-
led dosage. **Hydroxyzine HCl may potentiate barbiturates,
otics such as meperidine, and other CNS depressants.** In con-
ive use, dosage for these drugs should be decreased as much
%. Because drowsiness may occur, patients should be cau-
d against driving a car or operating dangerous machinery.
nteral Solution Precautions and contraindications: This dos-
form is intended only for I.M. or I.V. administration and
ld not, under any circumstances, be injected subcutaneously
tra-arterially. When the usual precautions for I.M. injection
been followed, reports of soft tissue reactions have been
When used intravenously, if given undiluted, minimal amounts
emalysis (2-3 grams of liberated hemoglobin) will occur. If
ed with 50 cc. of normal saline and given during a period of
minutes or more, this phenomenon does not occur. Due to the
e, and infrequent phlebitis, the rate of injection must not
ed 25 mg. per minute. A single I.V. administration in excess of
mg. is not recommended. Particular care should be used to
e injection only into intact veins; a few instances of digital
grene occurring distal to the injection site have been attributed
advertent intra-arterial injection or periarterial extravasa-
both of which should be avoided. **Use in Pregnancy:** When
inistered to rats at high dosage, hydroxyzine induced fetal
ormalities. Until human clinical data are available adequate
stablish safety in early pregnancy, hydroxyzine is contraindi-
d in early pregnancy.

Community Health Week October 16 to 22

The fourth annual Community Health Week, a public service program dedicated to improving individual and community health, will be October 16 to 22, James Z. Appel, president of the American Medical Association has announced.

Sponsored by the AMA, Community Health Week programs are carried out at the community level under leadership of state and local medical societies, in cooperation with the community's health workers.

Dr. Appel said 1966 programs will stress prevention and eradication of communicable diseases, and will emphasize the variety of challenging health careers open to young men and women.

"Teaming up for better health" is the continuing national theme for Community Health Week.

Skin Reactions From Perfume

The skin reactions some women get when they wear perfume in bright sunlight may be the fault of the perfume itself, rather than an "allergy."

Certain perfumes are compounds which produce phototoxic reactions, reports Kenneth H. Burdick, M.D., of the Department of Dermatology, Hitchcock Clinic and Dartmouth Medical School, Hanover, N.H. These reactions start as reddened areas, then turn to darkened skin spots which may last several months.

Some women don't react this way to perfume, however, because the outer layer of their skin—the stratum corneum—doesn't allow the perfume to penetrate.

Dr. Burdick removed small patches of this outermost skin layer on 10 volunteers, applied perfume to the skin, and exposed it to strong ultraviolet light.

In all 10 cases, phototoxic reactions occurred on the stripped-skin areas. Some darkening began within 15 minutes; severe reddening began within 24 hours and reached a peak 72 hours after the perfume was applied.

The rash then subsided, leaving varying amounts of skin pigmentation, or darkening. Three persons also had mild reactions on unstripped areas of skin which had been painted with perfume.

These reactions are typical of the furocoumarin class of compounds, Dr. Burdick said, and tests indicated the phototoxic material in the perfume was of this group.

Manufacturers of perfumes and toiletries "would do well" to use similar tests before putting their products on the market, Dr. Burdick suggested. His report appeared in the April *Archives of Dermatology,* published by the AMA.

CLASSIFIED ADVERTISEMENTS

(Continued from Page 38)

PRACTICE WANTED

INTERESTED in purchasing active general practice with good potential. Box No. 760, California Medicine.

PRACTICE OPPORTUNITIES

DELTA WONDERLAND! See May SUNSET magazine. In need of a doctor; office space available; town of Isleton, Sacramento County. Full cooperation from County of Sacramento, City of Isleton, school, and Isleton Chamber of Commerce. W. R. Lothrop, P.O. Box 704, Isleton, California 95641.

INTERNIST—Excellent opportunity to take over busy practice of internal medicine in fine location, San Jose, California area. Physician leaving for position at nearby Veterans Administration Hospital. Please contact Box No. 730, California Medicine.

DILIGENT GENERAL PRACTITIONER, PEDIATRICIAN OR INTERNIST needed in new air-conditioned medical building which now has two GP's, an OB-GYN, dentist, and drug store. Located in East Bay near San Leandro. Suites are large; rent to start at $50 a month. Write to Box No. 745, California Medicine.

NEW SPECIALIST MEDICAL CENTER—Halfway between Berkeley and Richmond in residential Albany-El Cerrito community of 45,000. Adjacent to Rapid Transit Station and El Cerrito Plaza. Ready for occupancy December 1966. Physician owned. Tenants include all the specialists in the community: four internists, two surgeons, one pediatrician, one Ob-Gyn. Ideal for orthopedist, ENT, dermatologist, psychiatrist. Air-conditioned. Convenient to hospitals. Contact: Ephraim Kahn, M.D., Fairmount Medical Building, 6601 Fairmount Avenue, El Cerrito, California 94532.

MEDICAL WRITING

MEDICAL EDITORIAL SERVICE from first draft to completed manuscript, including transcription, revision, and editing. Ten years experience in preparation of medical manuscripts, more than six years in fields of Cardiology and Cardiovascular Surgery. Educational background includes pre-medicine, medical school, practical clinical and research experience. Discreet, efficient, prompt service to all investigators. Mrs. Joanne B. Navarro, Medical Editorial Service, 821 South 4th Street, Alhambra, California 91801. Phone: (213) 283-5904.

VACATIONS

CROWN VALLEY GUEST RANCH AND PACK STATION—HIGH SIERRA. Enjoy a unique vacation; elevation 8,000 feet; accessible only by horseback. Excellent stream and lake fishing, deer hunting. A family vacation in the grandeur of the Sierras; East of the Wishon Dam Area. Write for free brochure and rates. P. O. Box 224, Orange Cove, Fresno County, California 93646.

OFFICES FOR LEASE, RENT OR SALE

SANTA MARIA, CALIFORNIA—Well-planned, established medical-dental building for sale, or office for lease having laboratory and three examination rooms with built-in supply and instrument cabinets. Adjacent parking. R. A. Wooten, 425 South Broadway, Santa Maria 93454; phone (805) WA 5-3204.

SOUTH SAN FRANCISCO—Available August 1, 1966, a 2,200 sq. ft. medical suite with seven treatment rooms, three consultation rooms, large room for use as lab, darkroom, waiting room or business area; spacious storage space. Building has private parking lot. Contact: John Tocchini, 344 - 14th Street, San Francisco, California 94103. Phone: (415) 861-3660.

UNUSUAL OPPORTUNITY—MARIN COUNTY, CALIFORNIA—Modern medical building nearly completed in Corte Madera, just 20 minutes across the Golden Gate Bridge from San Francisco; only five minutes from Marin and Ross General Hospitals. Presently only ONE physician, a general practitioner, in this growing community of 9,000. Unquestionably a full-time practice can be established in record time. Opportunity to acquire equity available. Contact: Rudy Duering, 690 Market Street, San Francisco, California 94104. Phone: (415) 421-5053.

LOS GATOS, CALIFORNIA: Beautiful setting. Medical suite 1,000 sq. ft. in modern bungalow-style professional building; air-conditioned. Ample parking. Between two large shopping centers in fast growing residential area. Close to two hospitals. Excellent location for general practitioner or pediatrician. Write: Dr. C. R. Chamberlain, 751 Blossom Hill Road, Los Gatos, California 95030. Phone: (415) 356-6650.

MEDICAL SPACE FOR RENT in modern medical building with two internists and GP. Includes consultation, two examining rooms, small lab, nurses' and business area and waiting area. Medical laboratory in building. Rent reasonable. Adequate private parking, close to Palo Alto Stanford Hospital and medical school. Maurice R. Oliva, M.D., 445 Burgess Drive, Menlo Park, California.

CARMICHAEL, CALIFORNIA—Park Medical Building, 850 sq. ft. available in eight-suite building, surrounded by Oriental gardens. Excellent residential community northeast of Sacramento. Two new hospitals nearby. Radiologist and lab in building; pediatrician or internist needed since none in vicinity. Clarence W. Smith, M.D., 6945 Fair Oaks Boulevard, Carmichael; phone (916) IVanhoe 3-5011.

SANTA ANA—New medical suites available approximately August 1, 1966, conveniently adjacent to Santa Ana Community Hospital. Suite size 970 to 1,200 square feet. For leasing information contact: R. F. Kammerman, M.D., or R. F. Jones, M.D., 917 North Broadway, Santa Ana, California 92701; phone: (714) 547-5404.

LONG BEACH—LAKEWOOD: Right in the cultural center. Landscaped park, churches, schools, boys' club, YMCA; ¼ mile to hospital, library, post office, sheriff, and major Lakewood shopping center. Pediatrician, OB-GYN, GP moving to their own buildings. Three to 19 rooms available. No other medical building adjacent to cultural center. Generous parking, air-conditioned. Six months, ½ rate; 6 per cent financing available. Phone (213) NE 2-1921 or 631-2086. E. Bingham, 16611 Caress Avenue, Compton, California.

EAST SAN JOSE: Suite built to suit in new medical-dental building; approximately 1,200 sq ft. for rent. Ample off-street parking. Located near hospital facilities. George Frank, M.D., 2880 Story Road, San Jose, California 95127.

BIG BEAR LAKE—Completely equipped emergency clinic for lease, purchase, or salary; immediately available. Excellent income guaranteed from first day; little or no investment required. Raymond L. Beach, M.D., 362 Third Street, Laguna Beach, California—phone (714) 494-7539; weekends, Box 540, Big Bear Lake, California—phone (714) 866-4681.

(Continued on page 48)

PHYSICIAN PLACEMENT SERVICE

The California Medical Association offers free placement assistance through the Physician Placement Service, 693 Sutter Street, San Francisco, California 94102. This service is for the use of all physicians seeking practice opportunities in California and for CMA members who are seeking an assistant or associate. A bulletin is published every other month. Opportunities in the Bulletin must be sponsored by a CMA member, an accredited California hospital or responsible persons in a California community. The Bulletin does not carry listings describing real estate for sale or office space for rent or lease or blind listings with box numbers.

CLASSIFIED ADVERTISING RATES

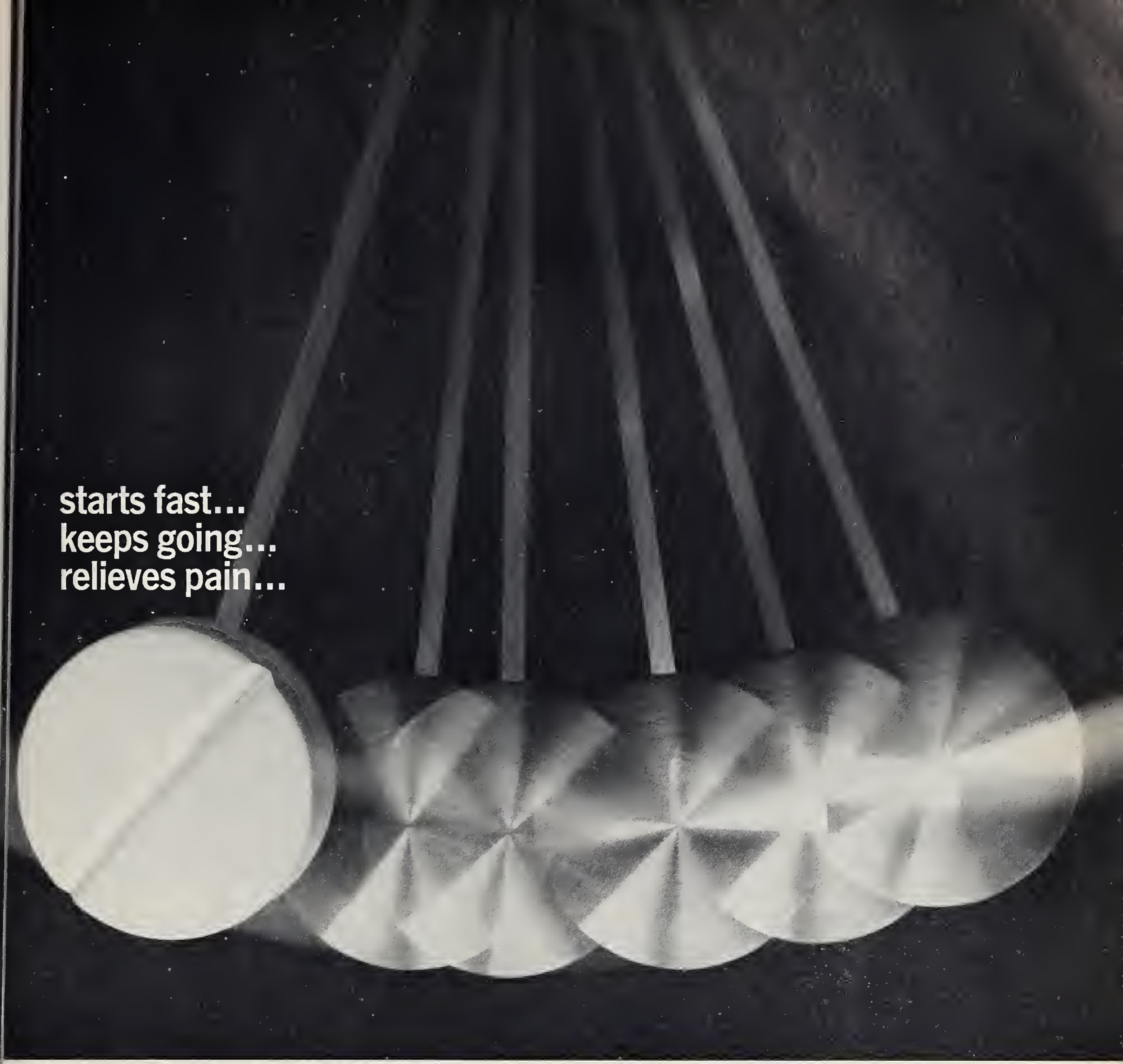
$10.00 for the first 50 words or less; 10c for each additional word thereafter. Box number charge: 50c for each month's insertion.

Copy for classified advertisements will be accepted through the fifth of the month preceding date of issue.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

USE ORDER BLANK ON PAGE 48 TO SEND IN YOUR

CLASSIFIED ADVERTISEMENTS



effective pain relief within 15 minutes...lasts 6 hours or more

PERCODAN relieves pain fast—usually within 15 minutes—and for prolonged periods, usually for 6 hours or more. Further, its speed and potency are *predictable* in the wide middle range of pain. PERCODAN is well tolerated and rarely causes constipation. **Usual Adult Dose:** 1 tablet every 6 hours. **Precautions:** The habit-forming potentialities of Percodan are somewhat less than those of morphine and somewhat greater than those of codeine. The usual precautions should be observed as with other opiate analgesics. Although generally well tolerated, Percodan may cause nausea, emesis or constipation in some patients. Percodan should be used with caution in patients with known idiosyncrasies to aspirin or phenacetin, and in those with blood dyscrasias. *Literature on request.*

PERCODAN®

Each scored yellow Percodan Tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit-forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine. U. S. Pats. 2,628,185 and 2,907,768

ENDO LABORATORIES INC., Garden City, New York Endo®

Heredity and Environment In Leukemia and Lymphoma

A group of Nebraska families has been identified in which the malignant diseases leukemia and lymphoma occur two and a half times as frequently as in a control group from the same area.

This suggests that susceptibility to these somewhat similar diseases may be inherited, says an article in the July 4 *Journal of the American Medical Association.*

The authors point out that it is susceptibility to a disease that may be inherited—not the disease itself.

Viruses, pneumonia-like organisms, and other infectious agents have all been suspected as causes of human leukemia and lymphoma. Animals have been implicated as the carriers of these infectious agents.

The four physician-investigators from the University of Nebraska College of Medicine and the Eppley Institute for Cancer Research, Omaha, interviewed 92 families (with 1,532 members) in which at least one person had leukemia or lymphoma. They also interviewed 69 randomly selected families with 1,294 members; some of these contained leukemia-lymphoma victims, others did not.

All of the families were from rural, eastern Nebraska, and all shared a common characteristic: considerable association with farm animals. The investigators reasoned that if animal-carried agents are involved in leukemia and lymphoma, both study groups would have similar exposure.

It was relatively easy to trace family histories for several generations in the stable, close-knit farm communities, the physicians said.

They found evidence of malignancies in most of the families, but leukemia and lymphoma appeared two and a half times as often in families in which at least one other member was known to have had the disease.

Twenty-one families were found with "multiple involvement," meaning two or more cases of leukemia or lymphoma. Forty-nine persons in these families had one or the other of the diseases, and 76 additional relatives had other malignant diseases.

Thus, in the "high risk" families, 125 out of 544 members (23 per cent) were found to have suffered some kind of malignant disease. Among 71 persons whose families contained only one known case of lymphoma or leukemia, 41 had at least one blood relative with a diagnosis of other malignancy (148 of 988 family members, or 15 per cent).

Forty-nine of the 69 control families had at least one member with a diagnosis of malignancy (132 of 1,294 family members, or 12 per cent).

The physicians said their data best fit the hypothesis that some persons may acquire leukemia or lymphoma if (1) they have a certain kind of genetic constitution, and (2) the disease-causing agent is encountered at the proper time and place.

If viruses really are the causative agent, a person's genetic makeup "may have a great deal to do eventually with what happens" when the virus enters his environment, the authors said. They are Perry G. Rigby, M.D., Robert C. Rosenlof, M.D., Peyton T. Pratt, M.D., Henry M. Lemon, M.D.

Your public relations problem has been our prime consideration in collection procedures during two generations of ethical service to the Medical Profession.

*

THE DOCTORS BUSINESS BUREAU

Since 1916

821 MARKET ST., SAN FRANCISCO 94103
GArfield 1-0460

PARAMUS COIN EXCHANGE

The East's Largest Coin Exchange

OFFERS U.S. GOLD FOR YOUR FUTURE
ALL BRILLIANT UNCIRCULATED

$20 Gold pieces	
Liberty	$ 54.95
St. Gaudens	$ 54.95
$10 Gold pieces	
Liberty	$ 32.95
Indian	$ 52.95
$5 Gold pieces	
Liberty	$ 24.95
Indian	$ 32.95
$3 Gold pieces	
	$349.00
$2.50 Gold pieces	
Liberty	$ 52.95
Indian	$ 32.95
$1 Gold pieces	
Type 1	$ 49.95
Type 2	$250.00
Type 3	$ 75.00

SETS

Liberty Gold Type Set	**4 Coins**	**$159.95**
Indian Gold Type Set	**4 Coins**	**$169.95**

All Coins in Custom Plastic Cases

U. S. SILVER DOLLARS	Single	$2.00
BRILLIANT	Roll	$39.95
UNCIRCULATED	Bag	$1695.00

Gold and Silver Is Today's Best Investment

Paramus Coin Exchange **A.N.A. Member**
Bergen Mall Shopping Center
Paramus, N.J. 07652 **201-342-2600**
Gentlemen: Please ship the following:

Name__________
Address__________
City__________State__________
Bill My D.C. Acct. #__________
Bill My Amer. Exp. Acct. #__________
For other coin values send for free catalogue!

BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNOTATED BIBLIOGRAPHY ON CHILDHOOD SCHIZOPHRENIA—1955-1964—James R. Tilton, M.S., Research Associate, Marian K. DeMeyer, M.D., Director, and Lois Hendrickson Loew, M.S., Research Associate, Clinical Research Center for Early Childhood Schizophrenia, Indiana University Medical Center, Indianapolis, Indiana. Grune & Stratton, Inc., New York and London, 1966. 136 pages, $3.75 (Paperbound).

CARCINOMA OF THE ALIMENTARY TRACT—Etiology and Pathogenesis—Edited by Walter J. Burdette, A.B., A.M., Ph.D., M.D., Professor and Head of the Department of Surgery and Director of the Laboratory of Clinical Biology, University of Utah College of Medicine; Surgeon-in-Chief, Salt Lake County Hospital; Chief Surgical Consultant, Veterans Administration Hospital, Salt Lake City, Utah. University of Utah Press, Salt Lake City, Utah, 1965. 233 pages, no price quoted.

CURRENT DIAGNOSIS—A Biennial Volume of Clinical Diagnostic Methods and Evaluations—Edited by Howard F. Conn, M.D., Robert J. Clohecy, M.D., and Rex B. Conn, Jr., M.D. W. B. Saunders Company, Philadelphia, Pa., 1966. 843 pages, $19.00.

DEFEATING ALCOHOLISM THE FAIRVIEW WAY—Maxie C. Collins, B.A., Th.M. Whitmore Publishing Co., Philadelphia, 1966. 327 pages, $5.00.

DISEASES OF THE HEART—Third Edition—Charles K. Friedberg, M.D., Cardiologist to The Mount Sinai Hospital and Attending Physician for Cardiology; Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. Single Volume, $22.00, 1787 pp. Two-Volume Set, $26.00; Vol. 1, pp. 1-930; Vol. 2, pp. 931-1787. W. B. Saunders Company, Philadelphia, Pa., 1966.

FINE-NEEDLE ASPIRATION BIOPSY—Used as a Direct Adjunct in Clinical Diagnostic Work—by Nils Söderström, M.D., Professor of Medicine, Lund. Grune & Stratton, Inc., New York, 1966.

HANDBOOK OF CARDIOLOGY FOR NURSES—Fifth Edition—by Walter Modell, M.D., F.A.C.P., Doris R. Schwartz, M.A., R.N., Louise S. Hazeltine, M.A., R.N., and Frederic T. Kirkham, Jr., M.D. Springer Publishing Company, Inc., New York, 1966. 323 pages, $4.75.

IMMUNOPATHOLOGY—IVth International Symposium, held at Monte Carlo (Principality of Monaco) February 1965—Sponsored by the World Health Organization, the Council for International Organizations of Medical Sciences, and the National Foundation. Edited by Pierre Grabar, Paris, and Peter A. Miescher, New York. Grune & Stratton, Inc., New York, 1966. 467 pages $19.75.

LAWS GOVERNING HOSPITALIZATION OF THE MENTALLY ILL—Volume VI, Report No. 61, May 1966—Formulated by the Committee on Psychiatry and the Law, published by the Group for the Advancement of Psychiatry, 104 East 25th St., New York, N.Y. 10010. 32 pages, 50 cents.

LITTLE STROKES—Walter C. Alvarez, M.D., D.Sc., Emeritus Professor of Medicine, University of Minnesota (Mayo Foundation). Foreword by Michael E. DeBakey, M.D. J. B. Lipincott Company, Philadelphia and Toronto, 1966. 190 pages, $8.00.

THE MAYO LEGACY—Gunther W. Nagel, M.D., Emeritus Clinical Professor of Surgery, Stanford University School of Medicine, Palo Alto, Calif. Charles C Thomas, Publisher, Springfield, Ill., 1966. 157 pages, $6.00.

METABOLIC TOXEMIA OF LATE PREGNANCY—A Disease of Malnutrition—Thomas H. Brewer, M.D., County Physician, Richmond Health Center, Richmond, Calif.; formerly, Instructor, Department of Obstetrics-Gynecology, University of California Medical Center, San Francisco, Calif. Charles C Thomas, Publisher, Springfield, Ill., 1966. 127 pages, $8.50.

PATHOLOGY, VOL. I & II—5th Edition—Edited by W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P., Professor of Pathology and Chairman of the Department of Pathology, University of Miami School of Medicine; Director of the Pathology Laboratories, Jackson Memorial Hospital, Miami, Florida. The C. V. Mosby Company, St. Louis, Mo., 1966. 1439 pages, $21.00.

PROGRESS IN CLINICAL PATHOLOGY—Volume I, A Review of Significant Advances in the Field of Clinical Pathology—Mario Stefanini, M.D., Editor, Chicago, Illinois. Grune & Stratton, Inc., New York 1966. 654 pages, $23.75.

PSYCHIATRIC DRUGS—Proceedings of a Research Conference Held in Boston—Philip Solomon, M.D., Editor. Grune & Stratton, Inc., New York, 1966. 262 pages, $9.75.

PSYCHIATRY IN THE PRACTICE OF MEDICINE—Allen J. Enelow, M.D., and Murray Wexler, Ph.D., University of Southern California School of Medicine. Oxford University Press, Inc., New York, 1966. 355 pages, $6.50.

PSYCHOTHERAPY AND THE BEHAVIORAL SCIENCES—Contributions of the Biological, Psychological, Social and Philosophic Fields to Psychotherapeutic Theory and Process—Lewis R. Wolberg, M.D., Dean and Medical Director, Postgraduate Center for Mental Health, and Clinical Professor of Psychiatry, New York Medical College, New York, N.Y. Grune & Stratton, Inc., New York, 1966. 198 pages, $6.75.

PULMONARY DISEASES AND ANOMALIES OF INFANCY AND CHILDHOOD—Their Diagnosis and Treatment—Milton I. Levine M.D., F.A.C.C.P., Attending Pediatrician, New York Hospital; Associate Professor of Clinical Pediatrics, Cornell University Medical College; Director, Pediatric Pulmonary Clinic, New York Hospital, New York City; and Armond V. Mascia, M.D., F.A.C.C.P., Assistant Attending Pediatrician, New York Hospital; Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Member, Pediatric Pulmonary Clinic, New York Hospital, New York City; Director, Pediatrics, Phelps Memorial Hospital, Tarrytown, New York. Hoeber Medical Division, Harper & Row, Publishers, New York and London, 1966. 368 pages, $12.00.

STRABISMUS—A Programmed Text—Robert D. Reinecke, M.D., Howe Laboratory of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary; and David Miller, M.D., Harvard Medical School, Massachusetts Eye and Ear Infirmary; with a foreword by Abraham Pollen, M.D. Appleton-Century-Crofts (Division of Meredith Publishing Company), New York, N.Y., 1966. 315 pages, $14.50.

SYMPOSIUM ON SURGERY OF THE OCULAR ADNEXA—Transactions of the New Orleans Academy of Ophthalmology—Arthur Gerard DeVoe, M.D.; Sidney A. Fox, M.D.; Howard Naquin, M.D.; T. E. Sanders, M.D.; Byron Smith, M.D.; Everett R. Veirs, M.D.; and Joseph A. C. Wadsworth, M.D. The C. V. Mosby Company, St. Louis, Mo., 1966. 245 pages, $16.00.

TREATMENT OF FRACTURES—Supplementary Volume to the 5th English Edition—By Prof. Dr. Lorenz Bohler, Director of the Accident Hospital, Vienna XX; Professor of Traumatology, University of Vienna; and Prof. Dr. Jorg Bohler, Director of the Accident Hospital, Linz; Professor of Traumatology, University of Vienna. Translated from the first German Edition by Alfred Wallner, M.D., Kalispell, Montana. Grune & Stratton, Inc., New York, N.Y., 1966. 402 pages, $28.75.

STACEY'S for any Medical Book in Print
Retail Stores in Palo Alto and San Francisco

NEW BOOK

CURRENT DIAGNOSIS. Edited by Howard F. Conn, M.D., Robert J. Clohecy, M.D., and Rex B. Conn, Jr., M.D. 843 pages. Illustrated. 1966. Saunders. $19.00. Here is a superb companion to the famous "Current Therapy" volume. To be published biennially, this new source spells out exact diagnostic methods and procedures for over 300 diseases and disorders. Signs and symptoms, course, physical findings, lab tests, complications and pitfalls are all covered.

Stacey's
326-9955
2575 HANOVER STREET
PALO ALTO, CALIFORNIA 94304

Please send me on approval:____________

Name____________
Street____________
City____________State____________

He's just supervised the harvesting of 1,200 acres of cotton and negotiated a water right of way with the Bureau of Reclamation.

Until he comes of age, Bank of America will help him make the right decisions. We're old hands at managing farm property. Throughout California, our experts have successfully run all types of agricultural operations: timber, dairy, vineyards, citrus, feeder lots, rice and row crops. And this same management service is available for your other investments too.

Whether you own a ranch or an apartment house, stocks or stores, if it needs constant attention, it could benefit from Bank of America's years of experience.

For information, stop in at any of our District Trust Offices, or see your local branch manager.

Bank of America
TRUST DEPARTMENT
BANK OF AMERICA NATIONAL TRUST & SAVINGS ASSOC.
MEMBER FEDERAL DEPOSIT INSURANCE CORPORATION

Thanks to Dexamyl®

brand of
dextroamphetamine
sulfate and amobarbital

she can say "No thank you" to the crêpes suzette.

'Dexamyl' does more than most anorectics. Because it curbs appetite *and* lifts mood, 'Dexamyl' can encourage the discouraged dieter to stay on her diet.

The mood lift with 'Dexamyl' can make the difference between the success or failure of her diet plan.

Formulas: Each 'Dexamyl' Spansule® Capsule (brand of sustained release capsule) No. 1 contains 10 mg. of Dexedrine® (brand of dextroamphetamine sulfate) and 1 gr. of amobarbital, derivative of barbituric acid [Warning, may be habit forming]. Each 'Dexamyl' *Spansule* capsule No. 2 contains 15 mg. of Dexedrine (brand of dextroamphetamine sulfate) and 1½ gr. of amobarbital [Warning, may be habit forming].

Principal cautions and side effects: Use with caution in patients hypersensitive to sympathomimetics or barbiturates and in coronary or cardiovascular disease or severe hypertension. Insomnia, excitability and increased motor activity are infrequent and ordinarily mild.

Before prescribing, see SK&F product Prescribing Information.

Smith Kline & French Laboratories SK&F

★

Specialized Service
IN
PROFESSIONAL LIABILITY
INSURANCE

is a high mark
of distinction

THE
MEDICAL PROTECTIVE COMPANY
FORT WAYNE, INDIANA
Professional Protection Exclusively since 1899

NORTHERN CALIFORNIA OFFICE:
Gordon C. Jones and John K. Galloway, Representatives
1518 Fifth Avenue, San Rafael, Telephone: 415-453-5140
Mailing Address: P.O. Box 1079, San Rafael 94902
SOUTHERN CALIFORNIA OFFICE:
Davis S. Spencer and Grady T. Dyer, Representatives
Suite 3, 33 East Huntington Drive, Arcadia, Tel. 213-681-5239
Mailing Address: P.O. Box 543, Arcadia 91008

Easy on
the Budget...
Easy on
the Mother

Tablets & Elixir
For Iron Deficiency Anemia

FAMOUS
Fergon®
brand of FERROUS GLUCONATE
C.M.A.P. CODE # 5261

BREON LABORATORIES INC.
Subsidiary of Sterling Drug Inc.
90 Park Avenue, New York, N.Y. 10016

Physicians Warn of Motorcycle Hazards

The motorcycle is creating a new epidemic in the United States, warn three physicians in the June 20 *Journal of the American Medical Association.*

Alarmed by the number and severity of motorcycle accidents in their own community, the three doctors from Portland, Maine, call for a campaign to reduce motorcycle deaths and injuries.

"It seems clear that the increasing popularity of small motorcycles is creating a serious health hazard in our communities," they said.

Part of the fault is driver carelessness, part is lack of safety devices, and part is due to the public's lack of awareness of special features of motorcycle handling, the physicians said.

"In motorcycle accidents, the victims have no protection whatever. Few helmets are used by the cyclists, and those in use are generally inadequate."

Head injuries are usually much more severe than those in auto accidents, and contaminated, compound fractures are more common, they noted.

"Victims are thrust, often at high speed, into another vehicle or to the pavement. The head receives the full force of impact when the cycle collides with another object, and the cyclist is catapulted over the handlebars."

The authors—two surgeons and a neurologist—saw the effects of such crashes on the patients they treated. From May through August last year, there were 38 victims of motorcycle accidents treated at Portland's Maine Medical Center.

Three of these victims died. One is blind and paralyzed. Ten suffered fractures of the lower extremities. There were two spinal fractures, two pelvic fractures, two severe abdominal injuries, and nine cases of major injury to head and neck.

It was difficult to classify the damage in these accidents, the authors said, because so many victims suffered multiple injuries.

"A most distressing fact is that the group involved are young, otherwise healthy persons. This is not an epidemic involving the aged or the infirm—rather it involves a group of young, healthy people who must be regarded as a most important group in our society."

According to the U.S. Bureau of Vital Statistics, there were 882 motorcycle-accident deaths in 1963. It seems reasonable, the authors said, that there were "far more than a thousand" deaths in 1965.

States need to develop carefully supervised motorcycle driver-training programs, meaningful road tests, and rigid inspection and licensing rules, the physicians said.

"Educational programs in public schools, as

(Continued on Page 23)

tions and adverse reactions: The transitory drowsiness which
ccur with hydroxyzine HCl usually disappears spontaneously
w days with continued therapy, or is correctable by dosage
on. Dryness of the mouth may be seen with higher doses.
ntory motor activity, including rare instances of tremor and
sions, has been reported, usually on higher than recom-
d dosage. **Hydroxyzine HCl may potentiate barbiturates,
ics such as meperidine, and other CNS depressants.** In con-
e use, dosage for these drugs should be decreased as much
. Because drowsiness may occur, patients should be cau-
against driving a car or operating dangerous machinery.
eral Solution Precautions and contraindications: This dos-
orm is intended only for I.M. or I.V. administration and
not, under any circumstances, be injected subcutaneously
a-arterially. When the usual precautions for I.M. injection
been followed, reports of soft tissue reactions have been
When used intravenously, if given undiluted, minimal amounts
nalysis (2-3 grams of liberated hemoglobin) will occur. If
with 50 cc. of normal saline and given during a period of
inutes or more, this phenomenon does not occur. Due to the
and infrequent phlebitis, the rate of injection must not
25 mg. per minute. A single I.V. administration in excess of
. is not recommended. Particular care should be used to
injection only into intact veins; a few instances of digital
ene occurring distal to the injection site have been attributed
dvertent intra-arterial injection or periarterial extravasa-
oth of which should be avoided. **Use in Pregnancy:** When
stered to rats at high dosage, hydroxyzine induced fetal
malities. Until human clinical data are available adequate
blish safety in early pregnancy, hydroxyzine is contraindi-
in early pregnancy.

Suicides and the Weather

Does a change in the weather cause some disturbed people to commit suicide?

The question has long been controversial, and much of the evidence seems contradictory.

A report in a current publication of the American Medical Association notes an association, however, between changes in barometric pressure and suicides.

When 527 suicides in Philadelphia were studied, these things were noted:

Significantly more than the expected number of deaths were associated with daily barometric pressure changes of 0.35 inches or more, particularly with falling pressures.

White males under age 45 and nonwhite males of all ages were the groups which showed a significant association between suicide and weather change.

Significantly fewer than the expected number of suicides occurred when atmospheric pressure was between 29.80 and 30.20 inches and the relative humidity was between 60 and 95 per cent.

An editorial in the March 14 *Journal of the American Medical Association* points out that "it is difficult to determine the influence of meteorological changes on specific diseases; it is even more

(Continued on Page 26)

Physicians Warn of Motorcycle Hazards

(Continued from Page 20)

well as press and other news media campaigns are needed. Physicians should make themselves available to participate in such efforts in their communities.

"Ways to improve safety equipment should be sought. Universal use of crash helmets alone would undoubtedly reduce the severity of many injuries."

Multiple injuries are so common in motorcycle accidents that physicians should work in teams in caring for them, the authors said. Skilled, early treatment of severe central-nervous-system injuries and complicated extremity fractures can improve recovery chances, they said.

Finally, the physician noted another aspect of motorcycle crashes: "In many of our cases, parents were opposed to their children having such vehicles. After considerable pressure, the parents reluctantly agreed. When an accident occurred following such a situation, the psychological problems were tremendous."

Physicians should warn parents of the hazards in driving motorcycles, the authors said.

"Only by taking a firm position in combating this rising hazard to health can we expect to avert a great epidemic."

The authors are Richard C. Dillihunt, M.D., George L. Maltby, M.D., and Emerson H. Drake, M.D., all of the Maine Medical Center, Portland.

The Mediatric Age:

There is a growing senescent body of people on their way to malignant inactivity, who sorely need your interest and direction to help them back to a more active and useful life. There are medicines too, designed to help. One such has proved useful in clinical practice.

"A steroid-nutritional compound (Mediatric) was used in 100 patients to relieve some of the symptoms caused by degenerative changes of aging ... This therapy resulted in improvement of 75 per cent of the patients ..."

McNeill, A. J.: Clin. Med. *8*:518 (Mar.) 1961.

"Mediatric (steroid-nutritional compound) capsules, one a day, seem to give definite help to debilitated patients."

Arnold, E. T., Jr.: Geriatrics *12*:612 (Oct.) 1957.

"Nutritional and hormone bolstering of function in the aged may have a useful place in geriatrics."

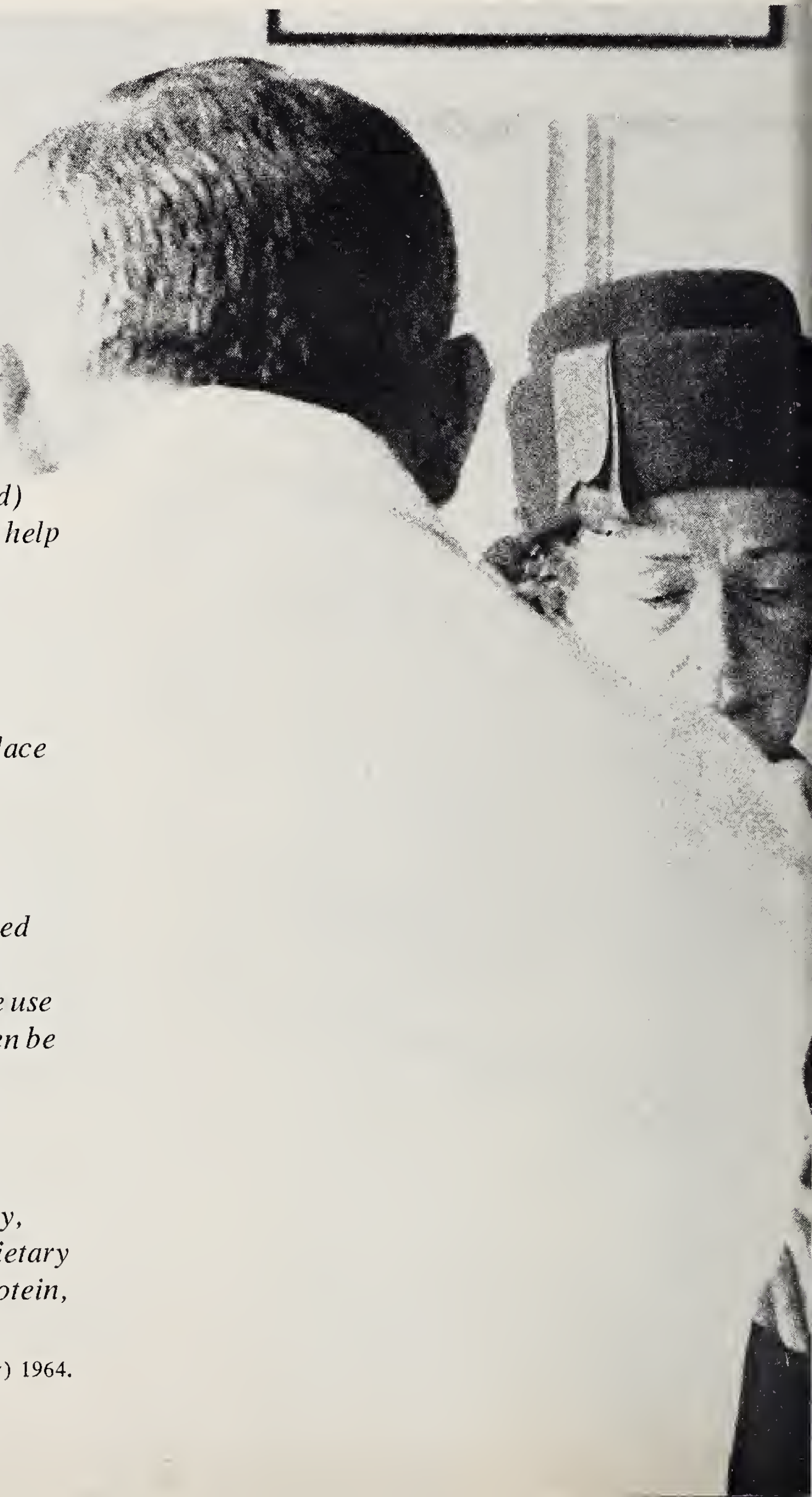
Morgan, A. F.: Gerontologist *2*:77 (June) 1962.

"In diets which for any reason are restricted in calories, enough of these substances (B vitamins) may not be supplied ... The use of B and C vitamin supplements may then be justified and indeed may be necessary."

Morgan, A. F.: Gerontologist *2*:77 (June) 1962.

"Intensive nutritional therapy is necessary, especially in elderly people, to correct dietary deficiencies created by large losses of protein, vitamins and other nutrients."

Riccitelli, M. L.: J. Am. Geriatrics Soc. *12*:489 (May) 1964.



Mediatric®

Designed for the "metabolically spent"

Nutritional reinforcement for those who can't – or won't – eat properly...balanced amounts of estrogen and androgen to counteract declining gonadal hormone secretion and its sequelae of premature degenerative changes...mild antidepressant for a gentle "mood" uplift...

The estrogen component in MEDIATRIC is PREMARIN® (conjugated estrogens—equine), the natural estrogen most widely prescribed for its superior physiologic and metabolic benefits.

MEDIATRIC also provides *nutritional reinforcement—blood-building factors and vitamin supplementation*. It contributes a *gentle "mood" uplift* through methamphetamine HCl.

Three different dosage forms—Liquid, Tablets, and Capsules—offer convenience and variety.

MEDIATRIC Liquid

Each 15 cc. (3 teaspoonfuls) contains:

*Conjugated estrogens—equine (Premarin®)	0.25 mg.
Methyltestosterone	2.5 mg.
Thiamine HCl	5.0 mg.
Cyanocobalamin	1.5 mcg.
Methamphetamine HCl	1.0 mg.

Contains 15% alcohol

MEDIATRIC Tablets and Capsules

Each MEDIATRIC Tablet or Capsule contains:

*Conjugated estrogens—equine (Premarin®)	0.25 mg.
Methyltestosterone	2.5 mg.
Ascorbic acid	100.0 mg.
Cyanocobalamin	2.5 mcg.
Intrinsic factor concentrate	8.0 mg.
Thiamine mononitrate	10.0 mg.
Riboflavin	5.0 mg.
Niacinamide	50.0 mg.
Pyridoxine HCl	3.0 mg.
Calc. pantothenate	20.0 mg.
Ferrous sulfate exsic.	30.0 mg.
Methamphetamine HCl	1.0 mg.

*Orally active, water-soluble conjugated estrogens derived from pregnant mares' urine and standardized in terms of the weight of active, water-soluble estrogen content.

MEDIATRIC helps keep the older patient alert and active; helps relieve general malaise, easy fatigability, vague pains in the bones and joints, loss of appetite, and lack of interest usually associated with declining gonadal hormone secretion.

CONTRAINDICATION: Carcinoma of the prostate, due to methyltestosterone component.

WARNING: Some patients with pernicious anemia may not respond to treatment with the Tablets or Capsules, nor is cessation of response predictable. Periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

SIDE EFFECTS: In addition to withdrawal bleeding, breast tenderness or hirsutism may occur.

SUGGESTED DOSAGES: *Male and female:* 3 teaspoonfuls of Liquid, 1 Tablet, or 1 Capsule, daily or as required.

In the female: To avoid continuous stimulation of breast and uterus, cyclic therapy is recommended (3 week regimen with 1 week rest period—Withdrawal bleeding may occur during this 1 week rest period).

In the male: A careful check should be made on the status of the prostate gland when therapy is given for protracted intervals.

SUPPLIED: No. 910 – MEDIATRIC Liquid, in bottles of 16 fluidounces and 1 gallon. No. 752 – MEDIATRIC Tablets, in bottles of 100 and 1,000. No. 252 – MEDIATRIC Capsules, in bottles of 30, 100, and 1,000.

16 fl. oz.
No. 910
MEDIATRIC
LIQUID
Ayerst
Each 15 cc. (3 teaspoonfuls) contains:
Contains 15% alcohol
SHAKE WELL BEFORE USING
CAUTION: Federal Law prohibits dispensing without prescription
MEDIATRIC
TABLETS

Mediatric®

steroid-nutritional compound

Ayerst®

AYERST LABORATORIES, NEW YORK, N.Y. 10017 • Montreal, Canada

6636

Serving
the Children
of the Nation
with . . .

Residential Treatment Programs

Day and Residential Camps

Day School Facilities

Behavioral Research

Professional Training Programs

DEVEREUX SCHOOLS

*serving mentally retarded
and emotionally disturbed children
and young adults*

UNDER THE DEVEREUX FOUNDATION

Helena T Devereux
Founder and Consultant

Edward L. French, Ph.D.
President and Director

FOR INFORMATION AND LITERATURE

Santa Barbara (Box 1079), California
Keith A. Seaton, Director of Admissions

Devon, Pennsylvania and Rutland, Massachusetts
Charles J. Fowler, Director of Admissions
Devereux Schools, Devon, Penna. 19333

Victoria (Box 2666), Texas
Richard D. Grant, Registrar

Suicides and the Weather

(Continued from Page 23)

difficult to determine the relationship between weather and suicides."

The authors of the report concede these things, and also point out that the number of suicides involved was small, because suicides occurred relatively infrequently.

"Still, the possibility of an association between certain changes in barometric pressure and suicide appears to exist," they say.

The authors are Edward Digon, M.Ph., and H. Barrett Bock, M.S., of the Division of the Biostatistics, Pennsylvania Department of Health, Harrisburg. Their report appears in the March issue of the *Archives of Environmental Health,* published by the AMA.

Ear-Bone Transplants Are Successful

It may someday be possible to restore hearing by transplanting tiny ear bones from one person to another.

The operation has been successfully performed on cats, and similar research is now underway in human ears, reports a recent publication of the American Medical Association.

It's difficult to reconstruct the chain of bones in the "middle ear" of a person with impaired hearing. The task would be easier if a physician could withdraw a bone from a storage bank and implant it in the damaged ear.

This sort of operation was performed on 10 cats by three physicians at the Mayo Clinic and Foundation and the University of Minnesota School of Medicine, Rochester. Their report appears in the June *Archives of Otolaryngology,* published by the AMA.

The anvil-shaped bone of the middle ear, the incus, was removed from cats' ears, and then implanted in other animals. In one case, a bone was successfully reimplanted in the same cat.

The transplants were found to be well tolerated when some were examined five to six months later. New bone had started to grow. This new bone was rapidly replacing transplanted bone by a process the authors called "creeping substitution."

Incus autografts—that is, transplants of middle ear-bones from one ear to another in the same person or animal—have been done several times. These new experiments suggest that transplants may be possible from one person to another. It is their impression, the authors said, that the bones not only grow well, but can function as part of the hearing mechanism.

The authors of the report are David F. Wilson, M.D., Jack L. Pulec, M.D., and Peter D. Van Vliet, M.D.

A "Standby" Heart Pacemaker

Development of an electronic pacemaker that stands by when a patient's heart is working normally, but takes over when the beat falters, is reported in the May 30 *Journal of the American Medical Association.*

The standby pacemaker is designed to overcome one difficulty of electronic heart stimulators: the "competition" between the heart's regular pulse and the pulse induced by a pacemaker operating at another rate.

This new pacemaker keeps a heart beating at a steady 69 beats a minute, give or take a beat or two. It goes into action only if the pulse becomes weak or irregular. The pacemaker shuts itself off when it senses that the heart is capable of maintaining its own rhythm. The pacemaker also lets the heart take over when the body needs a faster pulse rate.

The preliminary report from four investigators at Beth Israel Hospital, Newark, N.J., tells of generally good results for 17 patients.

Five persons have had standby pacers permanently implanted, and three of these have been working for up to four months. The one "partial failure" was in the first patient treated.

The remaining 12 persons used external, temporary units for brief periods. One of these patients was paced without difficulty for three months. The others used external pacemakers for only a few days while awaiting implantation of other types of permanent units.

The pacemaker has a sensing circuit which "listens" for the closing of the heart's ventricles. It is this electrical impulse which produces the so-called R wave, the highest rising wave on an electrocardiogram of a normal heart.

So long as these R-wave signals are strong and steady, the pacemaker does nothing. If the beat becomes weak or irregular, the unit goes into action.

So far, the patients who have received standby pacing have been victims of certain types of heart block, or Adams-Stokes disease. This is a condition in which the heart's atrial and ventricular chambers beat independently of each other. One symptom is frequent fainting or dizziness.

If the standby pacemaker's reliability is proved in further tests, it may be suitable for all types of heart patients, the authors said. They are Victor Parsonnet, M.D., I. Richard Zucker, M.D., Lawrence Gilbert, M.D., and George H. Meyers, Ph.D., Sc.D.

THE BLUE CHIP
STOCK
In Generic Pharmaceuticals

Towne
ASSURANCE
OF OPTIMUM
CLINICAL
EFFECTIVENESS

Pharmacies everywhere now stock TOWNE generic pharmaceuticals. Prescribe TOWNE to assure your patients of consistent high quality and uniformity ...at sensible prices.

PARTIAL LIST OF PRODUCTS

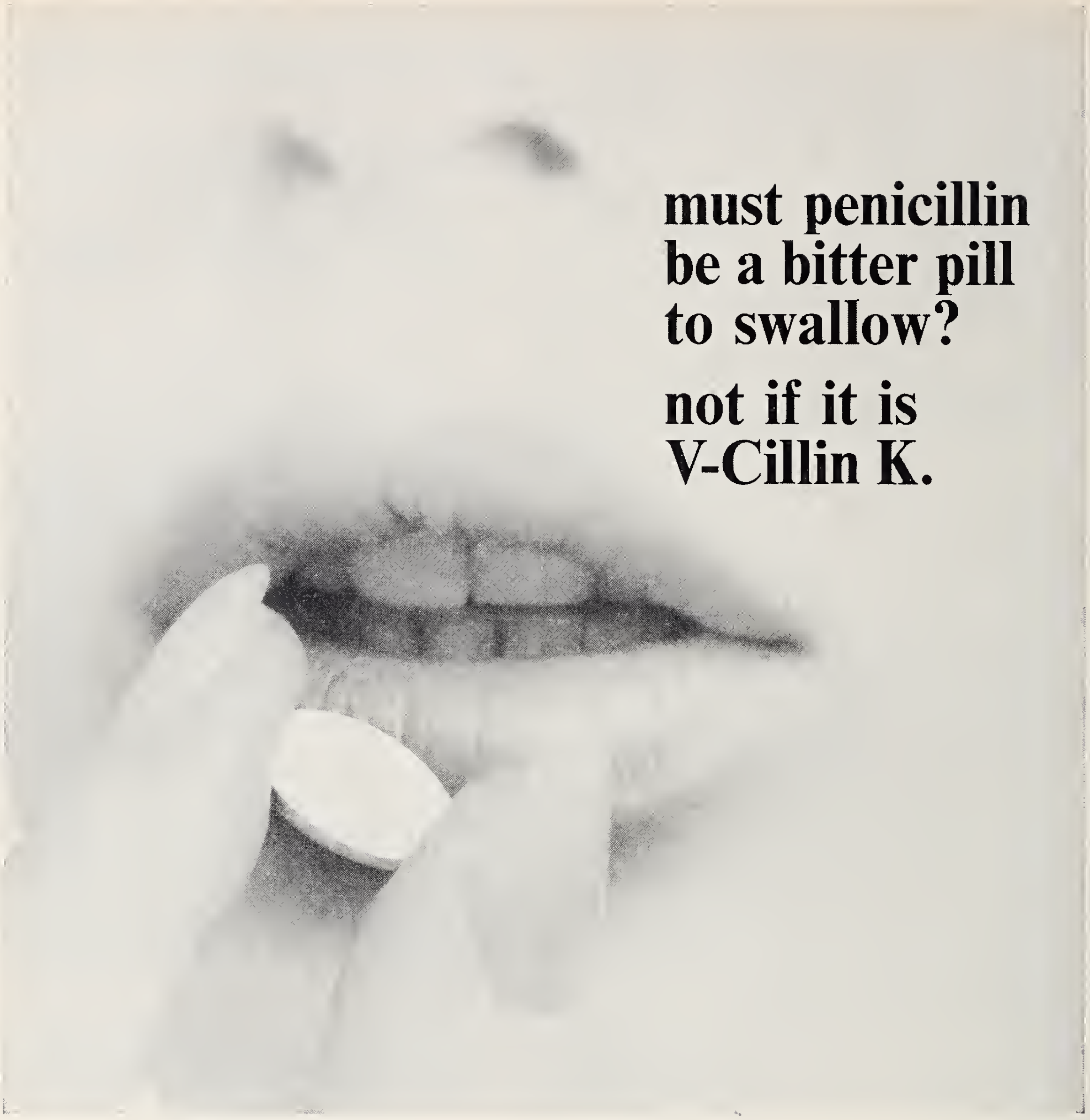
DIOCTYL SODIUM SULFOSUCCINATE N.F.
(S.G. capsules: 100mg–250mg)
HEPARIN INJECTION
(10M–20M–40M USP Units/cc)
C. T. MEPROBAMATE N.F.
(200mg–400mg)
C. T. PENICILLIN G USP
(200M–250M–400M Units)
C. T. PREDNISONE USP
(2.5mg–5mg)
C. T. QUINIDINE USP
(3 gr.)
C. T. RESERPINE USP
(0.1mg–0.25mg–1mg)
TETRACYCLINE HCL USP
(H.S. capsules–250mg–Domestic material)

Product List available on request.

Towne PRESCRIPTION PRODUCTS DIVISION

Towne, Paulsen & Company, Inc.

Pharmaceutical Chemists Monrovia, California



must penicillin be a bitter pill to swallow?
not if it is V-Cillin K.

V-Cillin K now has a unique glossy coating that banishes bitter penicillin taste and makes it easier to swallow. Within six seconds (just long enough for the tablet to get past the taste buds), the coating dissolves and the penicillin is ready for immediate absorption into the bloodstream. The patient still gets all the special benefits of V-Cillin K, including consistent dependability . . . even in the presence of food.

Indications: V-Cillin K is an antibiotic useful in the treatment of infections caused by streptococci, pneumococci, and sensitive strains of staphylococci.

Contraindications and Precautions: Although sensitivity reactions are much less common after oral than after parenteral administration, V-Cillin K should not be administered to patients with a history of allergy to penicillin. As with any antibiotic, observation for overgrowth of nonsusceptible organisms during treatment is important.

Usual Dosage Range: 125 mg. (200,000 units) three times a day to 250 mg. every four hours.

Supplied: Tablets V-Cillin K, 125 or 250 mg.; also, V-Cillin K, Pediatric, 125 mg. per 5-cc. teaspoonful, in 40, 80, and 150-cc.-size packages.

V-Cillin K® **Six-Second Barrier to Bitterness**

Potassium Phenoxymethyl Penicillin

600802

Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206.

Lilly

California
Medicine

Hemolytic Disease of the Newborn

Review of Deaths in California

EARL SIEGEL, M.D., *Chapel Hill, North Carolina;* ROBERT F. CHINNOCK, M.D., *Loma Linda;* CAROL B. HYMAN, M.D., *Los Angeles;* JOSEPH H. KUSHNER, M.D., *San Francisco;* TALCOTT BATES, M.D., *Monterey;* ARLINE LEWIS, M.P.H., AND ARNOLD GILBERT, M.D., *Berkeley,* AND LESLIE CORSA, JR., M.D., *Ann Arbor, Michigan*

■ *In order to find ways to decrease mortality from hemolytic disease of the newborn, a study was undertaken by physicians of the California Medical Association in cooperation with the California State Department of Public Health. Neonatal deaths during a two and a half year period were investigated and analyzed by review committees with the view of evaluating presumed deficiencies in management.*

The findings indicate that proper prenatal prediction and preparation by the physician for the management of HDN *calls for earlier and more comprehensive use of warning signals, as well as a constant reappraisal of current technology. New advances in the management of* HDN *require increasingly close cooperation between patients, their physicians and consultants.*

A COOPERATIVE STUDY, representing an extension of the previously reported California Maternal Mortality Study[18,19] was undertaken by physicians from the California Medical Association and the State Department of Public Health. The study's purpose was the reduction of mortality from hemolytic disease of the newborn (HDN). These physicians investigated and reviewed fatal cases of HDN that occurred in California during the period 1961-63.

In order to determine whether HDN would be a suitable disease for study, fatal cases of HDN that had occurred over a preceding two-year period were reviewed. From this preliminary survey, intensive study of HDN as a cause of neonatal death was considered to be feasible and desirable because: (a) HDN was a discrete clinical entity which could be identified from the death certificate; (b) approximately 200 such deaths occurred annually in California, a number that would lend itself to this type of study and probable significant statistical analysis; and (c) medical management of this condition might be improved by dissemination of information obtained from such a study.

Methods

For the study, the State of California was divided into three geographical regions—Northern California, Southern California excluding Los Angeles County, and Los Angeles County. A chairman was selected for each region and a panel of 77 physicians, including general practitioners, obstetricians, pediatricians, hematologists, pathologists and Public Health physicians served as investigating and reviewing consultants (Appendix A).

From the Committee on Maternal Child Care, California Medical Association and Bureau of Maternal and Child Health, State Department of Health.

Submitted 10 June 1966.

Reprint requests to: Committee on Maternal and Child Care, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

TABLE 1.—*Cases of HDN Assigned for Study from Death Certificates 1 July 1961 to 31 December 1963*

	Total Deaths	*With Autopsy*	
		Number	*Per Cent*
Death certificates mentioning hemolytic disease of the newborn	399	282	71
Underlying cause of death[1]	369	255	69
Listed on certificate but not underlying cause of death	30	27	90
Total cases assigned—	399	282	71
Excluded:	71	56	79
Not hemolytic disease of the newborn (determined by special consultant, committee chairmen, or committee review)	46	38	83
Other reasons	25	18	72
Included in study report:	328	226	69
Hemolytic disease of the newborn underlying cause of death[2]	289	201	70
Hemolytic disease of the newborn underlying cause of death on certificate also	280	193	69
Hemolytic disease of the newborn only mentioned on death certificate	9	8	a
Hemolytic disease of the newborn present in case but not underlying cause[2]	39	25	64
Hemolytic disease of the newborn was underlying cause of death on certificate	31	18	58
Hemolytic disease of the newborn not underlying cause of death	8	7	a

[1] Death certificate coded to International Classification of Disease—List Number 770.

[2] As determined by review committee.

[a] Per cent not computed for less than 10 deaths.

Cases were identified from death certificates registered with the State Department of Public Health. Infant deaths before 28 days of age during the two and a half year period from 1 July 1961 through December 1963 were selected for study whenever HDN or a synonym (International Classification of Diseases, Code 770) was mentioned, either as an underlying cause of death or as a contributing condition.

Each case was assigned to one of the investigating consultants who had been selected for his interest in HDN. Before each case investigation, permission was obtained from the attending physician. The consultant reviewed hospital records and interviewed physicians, nurses and technicians concerned with the care of the mother and infant. Using the information thus obtained, he completed a standardized form covering over 135 specific items, with additional space provided for comments. Postmortem reports and microscopic slides were utilized when available. The completed forms were distributed to the committee members who met periodically to review the cases.

The committees reviewed cases in a pilot study from 1 July 1961 to 31 December 1961. They reviewed 60 such cases before they felt they had sufficient background experience to make consistent, valid determinations and to begin tabulation for the study. At the beginning of the study the committees decided that idealized, theoretical standards had to be established for purposes of comparison. It therefore was assumed for each case reviewed that all current medical knowledge, technology, personnel and facilities were available. As a study tool, a list of all of the factors involved in the total management of HDN was devised and was called the list of "contributing factors." This list of contributing factors is included as Appendix B.

From their systematic review of each case, the committees determined: (a) The cause of death and the relative responsibility of HDN for it; (b) the possible preventability of the death; and (c) the various contributing factors which were present in each case. Decisions regarding contributing factors in management were made regardless of whether or not the death was considered possibly preventable. Contributing factors were divided into four major categories of responsibility relating to patient, hospital, laboratory or physician. In addition, each contributing factor was graded and recorded by the committee as:

Definite—when there was sufficient information, evidence and committee agreement on the existence of the contributing factor;

Questionable—when evidence was inadequate, so that a clear-cut decision regarding the existence of the contributing factor could not be made despite apparent shortcomings in care;

TABLE 2.—*HDN Responsibility for Death*

	Number	*Per Cent*
Total deaths studied	328	100
HDN responsibility for death:		
Directly	259	79
Indirectly	42	13
Indeterminate	11	3
Not responsible	16	5

Absent—when there was nothing to suggest the existence of a contributing factor;

Unknown—when information pertaining to the contributing factor was unavailable to the Committee.

The "definite" and "questionable" factors were combined by the committee in their eventual tabulation since "questionable" decisions represented apparent shortcomings in care; the "absent" and "unknown" categories were also combined.

Results

Cause of death (Table 1): In 46 of the 399 cases initially obtained from death certificate information, death was not considered to be due to HDN. In another 25 cases, other criteria were not met (for example, case under litigation, review was not completed or insufficient information obtained). HDN was accepted as the correct, verifiable diagnosis in the remaining 328 cases. In 40 cases, the committees agreed that HDN was present but did not agree with the underlying cause of death as listed on the death certificate. These findings corroborate those of other investigators[2,6,20] who have studied the limitations of death certificate information.

TABLE 3.—*Preventability of Deaths from HDN*

	Number	*Per Cent*
Total deaths studied	328	100
Not preventable	131	40
Indeterminate	121	37
Possibly preventable	76	23

Responsibility of HDN for deaths (Table 2): HDN was judged *directly* responsible for the death in 259 cases (79 per cent), since death resulted from intervention which was elected or required by HDN or from a chain of events initiated by the disease. In 42 cases (13 per cent) the death was caused by a condition which was obviously aggravated by the physiological effects of HDN, and HDN was considered to be *indirectly* responsible for the death. In 11 cases (3 per cent), it was not possible to determine whether HDN had played any part in the death. In 16 cases (5 per cent), although HDN existed, it was judged to have played *no* role in the death.

Preventability of death (Table 3): Of the 328

TABLE 4.—*Contributing Factors Associated with Preventability of Death (Per Cent)**

		Death Possibly Preventable		
	Total (328 Cases)	*No: (131 Cases)*	*Indeterminate: (121 Cases)*	*Yes: (76 Cases)*
Total deaths studied	100	100	100	100
PATIENT FACTORS:	20	18	18	25
Inadequate prenatal care	17	16	15	21
Medical advice not followed	6	5	7	9
Information not available	3	2	3	4
HOSPITAL (exclusive of Laboratory):	63	52	74	67
No prenatal history in delivery suite	17	13	19	18
Other record deficiency	24	18	29	26
No standard for HDN management	41	31	49	47
Inadequate exchange facilities	12	8	17	11
No review by perinatal committee	21	15	23	29
Other procedural deficiencies	15	7	22	17
LABORATORY:	35	28	32	49
Personnel deficiencies	2	1	2	3
Facility or procedural inadequacy	4	2	3	7
Technical deficiency	18	10	21	28
Reporting or interpretative deficiency	11	14	8	11
Other deficiencies	7	5	8	9
PHYSICIAN FACTORS:	94	85	99	100
Relating to infant	86	73	92	99
Preparation	19	14	22	25
Diagnosis	44	43	46	43
Therapy	75	50	88	97
Relating to mother	85	79	88	90
Inadequate or incomplete history	13	11	10	24
Diagnosis	74	64	82	76
Therapy	65	52	72	78
No contributing factors	5	12	.....	.....

---

*Percentages do not add to 100, for many cases had several contributing factors.

cases evaluated, 131 (40 per cent) were considered not preventable—regardless of the existence of several contributing factors or what was done during the prenatal, labor and delivery, or postnatal periods. The committees agreed that if idealized standards had been met, 76 (23 per cent) of the deaths would possibly have been prevented. One hundred twenty-one (37 per cent) of the cases were assigned to an "indeterminate" classification since possible preventability was questioned or disputed by the review committees.

Contributing factors in management (Table 4): Completely ideal management (with no contributing factors found) existed in only 16 cases (5 per cent). A few cases had a single contributing factor but in almost all cases more than one contributing factor was present. Some cases had one *"pivotal"* or *"crucial"* contributing factor that was mainly responsible for the fatal outcome, or was the principal reason for considering the death possibly preventable. These factors will be amplified in a later publication.

Patient factors appeared in 20 per cent of the cases. These factors were usually related to a mother who did not seek medical advice early enough in the gestation, or who did not follow the advice given.

Hospital factors were found in 63 per cent of cases. The most frequent contributing hospital factors were: (a) Prenatal history not available nor required to be in the delivery suite; (b) adequate records not required, for example, nurses' or physicians' notes; (c) failure to have a standard procedure for management of HDN; (d) inadequate exchange transfusion equipment available; and (e) absence of perinatal mortality committee or its equivalent to review the death.

Laboratory factors were identified in 35 per cent of the cases, usually technical difficulty or improperly reported laboratory data.

Contributing factors related to care by the *physician* were found in most of the cases (94 per cent). This high proportion resulted, in part, from the large number (47) of possible physician contributing factors which were listed and analyzed.

Contributing factors found in more than 20 per cent of cases (Table 5): Contributing factors were reclassified by their frequency. For simplicity, they were considered in three successive chronological phases: (1) Prediction and preparation for an affected infant; (2) management immediately before, during and after delivery of the infant; and (3) in relation to the exchange transfusion. These common contributing factors were then classified by the degree of their association with possibly preventable deaths compared with nonpreventable deaths. Those factors which, with statistical significance ($P<.05$), were associated with the possibly preventable deaths are preceded by an asterisk in the table.

The importance of the group of factors related to early prediction and preparation for an infant with HDN is substantiated by Table 5. These factors were the most common ones found in the study, and were also the largest group of factors significantly associated with possible preventability of death.

The group of common factors occurring immediately before delivery of the infant or before the first exchange transfusion was small. One rela-

TABLE 5.—*Common Contributing Factors in Management of HDN (Present in More Than 20 Per Cent of the 328 Cases)*

	Number	*Per Cent*
Total deaths studied	328	100
I. *Prediction and/or preparation for affected infant:*		
No paternal blood studies	176	53
*Titers (not done, insufficient number, etc.)	154	47
*Donor blood not crossmatched before delivery	139	42
No paternal genotype where pertinent	138	42
*No standards in hospital for HDN management	135	41
*No facilities for exchange prepared before delivery	115	35
*No qualified pediatrician notified in time	74	23
II. *Management before delivery or first exchange transfusion:*		
Hemoglobin or PCV not ordered when indicated	86	26
Bilirubin determination not ordered	66	20
III. *Exchange transfusion:*		
*Delay in initiation of exchange transfusion	128	39
*Inadequate monitoring of infant during exchange	71	21

*Associated with possibly preventable deaths $P<.05$.

tively uncommon factor, but one which was significantly associated with possible preventability of deaths, was inadequate communication between the consultant and the attending physician.

Among the deficiencies pertaining to the exchange, two were common: (1) Delay in starting the initial or repeat transfusion; and (2) inadequate monitoring of infant during exchange transfusion. Both were significantly associated with possibly preventable deaths.

Discussion

The data in this paper are unique in that they include deaths from HDN for a two and a half year period, and an evaluation of the management of HDN in all parts of a large state rather than at a single institution. However, interpretation of the findings of this study should take into consideration the large geographical area of California and the varied socioeconomic conditions that exist in the state. This is especially important, as these conditions were deliberately not evaluated by the review committees when they analyzed each case for contributing factors. It should also be reemphasized that the standards for management of HDN against which each case was judged assumed that *all* current medical knowledge, technical proficiency and facilities were available. Therefore, the study findings which are expressed as "contributing factors" (Appendix A) found cannot realistically be interpreted as an indictment of the management of HDN as it existed in 1961-63 in California but rather as a source of information to be analyzed and utilized for improvement of care.

The study had several other limitations. It dealt exclusively with neonatal mortality, not morbidity, utilized retrospective data, and judged possible preventability of death and contributing factors by arbitrary indices. If the study sample had been representative of *all* cases of HDN and not limited to fatal cases, the distribution and frequency of the various contributing factors would probably have been significantly different. The largest numbers of contributing factors would probably have been more concerned with the timing and technique of the first and subsequent exchange transfusions (as well as post-exchange care) rather than prenatal prediction and preparation.

On the other hand, had it been possible to study intrauterine deaths from HDN, the prenatal segment of care would have been emphasized. In California, for example, the number of *fetal* death certificates with HDN as underlying cause of death have exceeded the number of *neonatal* death certificates:

HDN Mortality (California)

	1962	*1963*
Fetal deaths	270	240
Neonatal deaths	171	154
Total	441	394

The relative importance of intrauterine deaths from HDN is also reported from two recent hospital studies. In an analysis of 1962 deliveries at New York Hospital,[7] the ratio of fetal deaths to neonatal deaths was 3:1. Boggs,[3] on the University of Pennsylvania obstetrical service, reported twice as many stillbirths as neonatal deaths.

The matter of prenatal prediction and preparation for HDN is further emphasized by the number of deaths in first affected infants. In the above New York Hospital series, among seven of 12 women who lost infants from HDN, it was their first immunized pregnancy.[7] We too found that neonatal deaths are not at all limited to mothers who previously delivered affected infants. Of the 264 cases in which information was available, over one-third (39 per cent) had no history of a previously affected infant. A full report on first immunized infants who were fatally involved will be presented in a future communication.

Several practices which were only beginning to be used in California during the study period 1961 to 1963, and therefore excluded in the committee reviews, are currently considered to be useful. Routine antibody screening was one of these practices, and was a subject of increasing concern to the committees, particularly since Pirofsky's[21] report on this aspect of management pointed out its value. Amniotic fluid examinations are now found to be of extreme value in the prediction of affected infants and the prediction of the severity of their disease.* Newer techniques to be considered and evaluated are repeated intrauterine transfusions,† intrauterine exchange transfusion,[1,9] and protection from maternal sensitization through the use of hyperimmune gamma globulin (high titer anti-D), at delivery.[10]

With an awareness of the common and significant contributing factors in the management of HDN, patients, physicians, hospitals and laboratories can make better plans to coordinate obstetric and pediatric care and thus improve perinatal outcome. The study findings indicate, especially, that proper prenatal prediction and preparation for the management of HDN demand wider and earlier use of warning signals currently available to physicians.

---

*Reference Nos. 8, 11-14, 17, 22, 24, 25.

†Reference Nos. 4, 5, 14-16, 23, 25.

Appendix A

MEMBERS OF REGIONAL COMMITTEES AND SPECIAL CONSULTANTS

Region I

Chairman: Joseph H. Kushner, M.D., San Francisco

Review Committee: *General Practice:* Joseph J. Alderson, M.D., San Anselmo; J. Lyman Hurlbut, M.D., Kentfield; John Leland, Jr., M.D., Berkeley. *Obstetrics:* R. Elgin Orcutt, M.D., San Francisco; Edward Prince, M.D., San Jose. *Pediatrics:* B. J. Siebenthal, M.D., Sacramento. *Pathology:* David Linder, M.D., San Francisco. *Public Health:* B. L. Zinnamon, M.D. (deceased), Santa Rosa.

Special Consultants (Pediatricians): Richard L. Anderson, M.D., Eureka; Talcott Bates, M.D., Monterey; Robert Black, M.D., Monterey; Robert Burnip, M.D., San Francisco; John Howard Carr, M.D., San Rafael; John Castiglione, M.D., Visalia; John B. Copeland, M.D., Chico; Eugene W. Earl, M.D., Redding; Russell Hansen, M.D., Woodland; William Waring, M.D., Ukiah; Jack G. Watkins, M.D., Roseville; Rex Whitworth, M.D., Salinas; Richard Leonards, M.D., San Francisco.

Region II

Chairman: Carol B. Hyman, M.D., Pediatric Hematology, Los Angeles

Review Committee: *General Practice:* Walter G. Case, M.D., San Fernando. *Obstetrics:* Frank A. M. Bryant, M.D., Napa; Peter R. Forbes, M.D., Van Nuys; Warren Moe, M.D., Los Angeles. *Pathology:* Robert S. Cleland, M.D., Los Angeles. *Pediatrics:* Harold Z. Brown, M.D., Beverly Hills; Joan E. Hodgman, M.D., Los Angeles; Miriam G. Wilson, M.D., Los Angeles.

Special Consultants (Pediatricians): Frank Dudenhoeffer, M.D., La Canada; Herbert Levin, M.D., Beverly Hills; Jerome Lipin, M.D., Los Angeles; John Marsden, M.D., Encino; Marvin Nierenberg, M.D., Encino; Donald Polhemus, M.D., Glendale; Richard Rosenstein, M.D., Encino; Earl B. Rubell, M.D., Van Nuys; Joseph Settelmayer, M.D., Whittier; Nomie A. Shore, M.D., Los Angeles; Carter R. Wright, Jr., M.D., Los Angeles; Harvey Shipper, M.D., Los Angeles; Kenneth O. Williams, M.D., Los Angeles.

Other Study Participants: Alonzo B. Cass, M.D., Beryl Graham, M.D., Lillian Kositza, M.D., Sakaye Shigekawa, M.D., Los Angeles; Phillip Sturgeon, M.D., Santa Monica; Ann Rose Wright, Los Angeles.

Region III

Chairman: Robert F. Chinnock, M.D., Los Angeles

Review Committee: *General Practice:* Frederick Allen, M.D., San Diego; John E. Haworth, M.D., El Centro. *Obstetrics:* James E. Sandell, M.D., San Diego; Harold F. Ziprick, M.D., National City. *Pediatrics:* J. Harold Batzle, M.D., Riverside; Lloyd G. Carnahan, M.D., Fullerton; George A. Chalfant, M.D., Alta Loma; Herman W. Hyatt, M.D., Bakersfield; C. Saybart Kinsell, M.D., Santa Barbara. *Pathology:* John J. Sheehy, M.D., Riverside. *Public Health:* Louis J. Needels, M.D., Santa Barbara.

Special Consultants (Pediatricians): Nils Bolduan, M.D., Santa Barbara; J. G. Calene, M.D., Santa Barbara; La Filse Chaney, Jr., M.D., Escondido; Nathaniel Cohen, M.D., Costa Mesa; Hunter Crittenden, M.D., Riverside; Richard R. Dooley, M.D., Riverside; Jeffrey Englehart, M.D., Buena Park; John Forney, M.D., Bakersfield; Murray T. Freeman, M.D., Redlands; J. Richard Hill, M.D., San Diego; Stanley Marabuyashi, M.D., Santa Ana; Sam Plaut, M.D., San Bernardino; Tom W. Robinson, M.D., Newport Beach; William H. Weinfurtner, M.D., Riverside; Edward W. Zeman, M.D., Riverside.

The authors also wish to gratefully acknowledge the generous editorial assistance of Miss Anne Schmid, Department of Pediatrics, University of California, San Francisco.

Appendix B

NEONATAL MORTALITY STUDY TRANSCRIPT SHEET—CONTRIBUTING FACTORS

Patient Factors (maternal and paternal):

1. Inadequate or no prenatal care obtained
2. Medical advice given but not followed
3. Information withheld by mother

Hospital Factors (exclusive of laboratory):

4. Prenatal history sheet or prenatal information (Rh, expected date of confinement, past history) not required to be in delivery suite
5. Or not complete
6. Adequate nurses' notes or physicians' notes not required
7. Standard procedure for management of HDN not available in hospital
8. Severe HDN (correctly predicted) allowed to deliver where facilities for exchange are inadequate
9. Perinatal mortality review committee did not review case
10. Nurses insufficiently trained in pertinent observation and techniques
11. Poor organization resulting in undue loss of time between delivery and initiation of exchange
12. Reports lost, delayed or erroneous

Physician Factors:

Obstetric

13. Incomplete past obstetrical or newborn history from mother
14. Failure to obtain necessary reproductive history from previous delivery attendants
15. Rh and ABO not performed on maternal blood
16. Rh or ABO not performed on paternal blood when indicated
17. Paternal genotype not attempted where pertinent

18. Indirect Coombs screen not done on "dangerous recipient," (*e.g.*, previous transfusions, unregistered mother, previously jaundiced infant)
19. Maternal antibody titers not done
20. Maternal antibody titers not done early enough
21. Maternal antibody titers insufficient in number
22. Failure to induce labor early when indicated
23. Failure to do cesarean section early when indicated
24. Early induction or cesarean section done when not indicated
25. Cesarean section performed before adequate trial of induction
26. Donor blood for exchange not cross matched against mother in advance of delivery when possible
27. Facilities for exchange transfusion not prepared in advance when severely involved infant should have been expected
28. Physician qualified to treat infant not notified in advance when possibly affected infant expected
29. Physician qualified to treat infant not notified in advance when probably affected infant expected
30. Failure to send maternal and cord blood to hospital to which infant was transferred for exchange transfusion
31. Improper analgesia or anesthesia
32. Inadequate communication, consultant to or from attending M.D.

Pediatric

PREPARATION

33. Not present at delivery when ample advance notification given
34. Proper blood (O Rh negative, fresh low titer, cross matched against mother) not available at delivery when sufficient notification given
35. Inadequate communication to hospital when infant transferred for exchange

DIAGNOSTIC DEFICIENCIES

Failure to order indicated tests on newborn infant:

36. Coombs, direct
37. Hemoglobin or PCV
38. Bilirubin, direct and total (indirect by calculation)
39. ABO type
40. Reticulocytes/100 RBC or nucleated RBC/100 WBC

THERAPEUTIC DEFICIENCIES

41. Failure to do exchange transfusion when indicated
42. Delay in initiation of initial or repeat exchange transfusion
43. Exchange transfusion performed when not indicated
44. Inadequate technical training or skill in performing exchange
45. Incompatible blood used
46. Old blood used (more than five days old)
47. Packed or sedimented cells not used when indicated
48. Insufficient attention to initial correction of cardiac failure before proceeding with exchange
49. Inadequate monitoring of infant during exchange transfusion
50. Assistant to monitor infant either unavailable or not competent
51. Excessive deficit during exchange
52. Excessive deficit after exchange
53. Insufficient deficit during exchange
54. Insufficient deficit after exchange
55. Improper use of IV albumin for exchange, *i.e.*, used when infant in failure or anemic
56. Improper supportive therapy (specify, *e.g.*, heat, O_2, calcium, digitalis, etc.)
57. Inadequate post-exchange care
58. Improper care not related to HDN (*e.g.*, improper resuscitation, isolation, drugs)
59. Overlooked or did not recognize pertinent data

LABORATORY FACTORS:

60. Personnel inadequately trained
61. Personnel not available when needed
62. Inadequate facilities available
63. Inadequate physical facilities and equipment
64. Errors in methodology or technique
65. Mistyping coated Rh positive infant typed as negative at birth
66. Direct Coombs improperly performed or interpreted
67. CBC on clotted blood
68. Maternal mistyping Rh negative as positive
69. Reliability of bilirubin questioned
70. Errors in reporting laboratory tests (specify, *e.g.*, titers not specified as albumin, saline or Coombs; direct Coombs test positive reported as negative)

REFERENCES

1. Adamsons, Jr., K., Freda, V. J., James, L. S., and Towell, M. E.: Prenatal treatment of erythroblastosis fetalis following hysterotomy, Ped., 35:848, 1965.

2. Bierman, J. M., Siegel, E., French, F. E., Connor, A.: Community impact of handicaps of prenatal and natal origin, Public Health Rep., 78:839, 1963.

3. Boggs, Jr., T. R.: Survival rates in Rh sensitizations; 140 interrupted versus 141 uninterrupted pregnancies, Ped., 33:758, 1964.

4. Bowman, J. M., and Friesen, R. F.: Multiple intraperitoneal transfusions of the fetus for erythroblastosis fetalis, New Engl. J. Med., 271:703, 1964.

5. Bowman, J. M., and Pollock, J. M.: Amniotic fluid spectrophotometry and early delivery in the management of erythroblastosis fetalis, Ped., 35:815, 1965.

6. Emery, J. L., Irvine, K. A.: Death certification of children, Brit. Med. J., 2:1510, 1958.

7. Erlandsen, M. E., and Haber, J. M.: Severe erythroblastosis fetalis in first immunized pregnancies, Am. J. Ob. Gyn., 90:779, 1964.

8. Freda, V. J.: The Rh problem in obstetrics and a new concept of its management using amniocentesis and spectrophotometric scanning of amniotic fluid, Am. J. Ob. Gyn., 92:341, 1965.

9. Freda, V. J., and Adamsons, Jr., K.: Exchange transfusion in utero, report of a case, Am. J. Ob. Gyn., 89:817, 1964.

10. Freda, V. J., Gorman, J. G., and Pollock, W.: Rh factor: Prevention of isoimmunization and clinical trial on mothers, Science, 151:28, 1966.

11. Lewis, F., Schulman, H., and Hayashi, T. T.:

Spectrophotometric analysis of amniotic fluid in erythroblastosis fetalis, J.A.M.A., 190:195, 1965.

12. Liley, A. W.: Liquor amnii analysis in the management of the pregnancy complicated by Rhesus sensitization, Am. J. Ob. Gyn., 82:1359, 1961.

13. Liley, A. W.: Errors in the assessment of hemolytic disease from amniotic fluid, Am. J. Ob. Gyn., 86:485, 1963.

14. Liley, A. W.: The use of amniocentesis and fetal transfusion in erythroblastosis fetalis, Ped., 35:836, 1965.

15. Liley, A. W.: Intrauterine transfusion of foetus in haemolytic disease, Brit. M. J., 2:1107, 1963.

16. McCrostie, H. H.: Intrauterine transfusion of the foetus in haemolytic disease, Brit. M. J., 1:885, 1964.

17. Misenhimer, H. R.: Amniotic fluid analysis in prenatal diagnosis of erythroblastosis fetalis, Ob. Gyn., 23:485, 1964.

18. Montgomery, T. A., and Lewis, A: Maternal and perinatal deaths in California, Calif. Med., 93:302, 1960.

19. Montgomery, T. A., Lewis, A., Hammersly, M.: Maternal deaths in California, 1957-1962, Calif. Med., 6:412, 1964.

20. Montgomery, T. A., Lewis, A., Hammes, L.: Live birth certificates—evaluation of medical and health data in California, Calif. Med., 96:190, 1962.

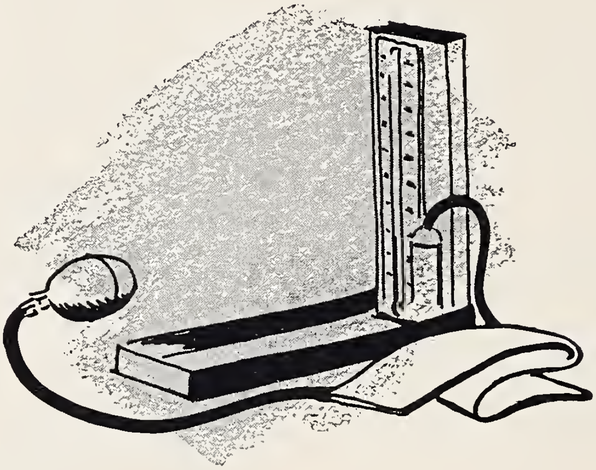
21. Pirofsky, B.: Erythroblastosis—a changing serologic problem, Am. J. Ob. Gyn., 92:720, 1965.

22. Queenan, J. T., and Adams, D. W.: Amniocentesis for prenatal diagnosis of erythroblastosis fetalis, Ob. Gyn., 25:302, 1965.

23. Queenan, J. T., and Douglas, R. G.: Intrauterine transfusions: a preliminary report, Ob. Gyn., 25:308, 1965.

24. Smith, C. H.: Crossing the chorion: amniocentesis, J. Ped., 65:642, 1964.

25. Westberg, J. A., and Margolis, A. J.: Amniotic fluid evaluation and intrauterine transfusions for erythroblastosis fetalis, Am. J. Ob. Gyn., 92:583, 1965.



Tokyo-Yokohama Asthma

A Review and Some Current Concepts

REXFORD G. HAYCRAFT, LIEUTENANT COLONEL, MC, USAF
Offutt Air Force Base, Nebraska

■ *Soon after the occupation of Japan, military physicians began recording an unusually large number of patients with asthma. Subsequent reports labeled the condition "Yokohama asthma" and called it a new environmental respiratory disease. It occurred in the Tokyo-Yokohama area, in previously healthy persons, from October to May during the time of the heaviest concentration of air pollution.*

The disease begins with cough at night, wheezing and shortness of breath, and apparently does not respond to the usual forms of treatment for asthma. It was reported that the symptoms subsided upon removal of the patient from the Tokyo-Yokohama area but abruptly recurred upon return to the area. It has been implied that the disease is a hypersensitivity phenomenon due to some unknown contaminant in the atmosphere. More recent studies indicate that Tokyo-Yokohama asthma is not a disease but a syndrome seen in people with bronchial infections and asthma. The high level of air pollution is thought to have an aggravating rather than a sensitizing effect.

IN THE AUTUMN OF 1946 clinicians at the United States Army Hospital in Yokohama began reporting an unusually large number of cases of asthma among our military personnel. Huber[3] in 1954 published a preliminary report describing a new environmental respiratory disease which was popularly termed "Yokohama asthma." The condition, which was manifested by nocturnal cough, wheezing and dyspnea, usually occurred in the autumn and winter in previously healthy persons. Apparently the usual therapeutic regimen for asthma was ineffective. Removal of the patient from the area gave prompt and permanent relief from the symptoms but the symptoms would recur if the patient returned to the area. This entity was later described and reported by Phelps[5,6,7] and Smith.[9]

At first it was thought that the condition was due to some local allergen but in extensive studies no evidence was found that any pollen was the cause, and investigations of the air contaminants failed to isolate any causative agent. Important studies by the Armed Forces Epidemiology Board are continuing. Most observers have come to believe that the condition is related to the heavy pollution of the air in the Kanto Plain area.

Kanto Plain

At first this asthmatic condition was reported to occur only in and close about Yokohama, but as our troops became located at other areas and as Japanese industry continued to grow, the respiratory condition began to occur throughout the Kanto Plain area, of which Yokohama occupies a small part.

The Kanto Plain is meteorologically unique with mountain barriers to the north and west and the

---

Presented before the Section on Allergy at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 865th Medical Group, Offutt Air Force Base, Nebraska 68113.

ocean to the south and east. A winter monsoon develops with a large northerly current of continental polar air on the east of the main Asiatic high. The presence of this winter monsoon tends to produce air stability. This climatic condition predisposes to heavy pollution of the air at ground level, especially during the winter months and at night.

Smith[9] studied the incidence of Tokyo-Yokohama asthma as related to meteorological conditions and concluded that a clear-cut meteorological system correlates extremely well with the peak incidence of Tokyo-Yokohama asthma. The condition occurs in other heavy industrial areas in Japan, particularly in Osaka. Toyama[12] reported that 20 per cent of the Japanese population is exposed to air pollution. In his study of large groups of Japanese school children he concluded that a higher incidence of pulmonary disease existed in those exposed to higher air pollution.

The Clinical Course

As previously reported, the typical patient was a generally healthy adult without previous asthma or allergic disease. On his first or second autumn in the Kanto Plain area he would develop chronic nocturnal cough, wheezing and shortness of breath. These symptoms usually responded poorly to standard treatment with bronchodilators and not at all to antihistamines. The disease progressed until the patient was symptomatic throughout the day and became severely incapacitated. Pulmonary function studies revealed persistent obstruction of flow of air. The severity of the disease varies between individuals; in some it never comes to a full development of the symptoms while in others it progresses in severity until the patient has to be removed from the area.

At first it was reported that all the patients had dramatic and permanent relief of symptoms as soon as they were out of the area. Later follow-up studies by Phelps,[5] however, revealed that some patients continued to have symptoms and some even became worse after they left the Kanto Plain. Therefore, it was postulated that if a patient with symptoms remained in the area too long, he might have permanent lung damage. There may be weakness in this argument because none of these patients were studied until symptoms developed and thus they may already have had pulmonary disease such as chronic bronchitis or emphysema.

Recent Studies

Spotnitz[10,11] studied a large number of patients (1 July 1963-30 June 1964) at Zama U.S. Army Hospital, Japan, who were suspected of having asthma or bronchitis. They were considered to have Tokyo-Yokohama asthma if their first symptoms did not develop until after they arrived in the area. These patients were intensively studied, the studies including a most detailed history, x-ray films, differential leukocyte counts, sputum culture, sputum smears for eosinophiles and spirometric studies before and after isoproterenol nebulization. Frequent follow-up studies were done. There were 237 patients on whom sufficient information for analysis was available. The disease of highest incidence (89 patients) was acute bronchitis. The history in this group was quite diagnostic, beginning with the symptoms of a cold which progressed to an associated cough with mucopurulent sputum. The symptoms tended to persist and a large number of this group complained of wheezing and cough, and of awakening from sleep usually between 1 and 3 a.m. These patients responded to bronchodilators and the disease was usually self-limiting, lasting two to four weeks. Spirometric measurements were abnormal in 45 per cent of this group at first, but in all cases returned to normal during follow-up. In 92 per cent of this group the leukocyte differential showed less than 5 per cent eosinophiles. It was felt that the disease was like bronchitis anywhere else in the world except more severe and persistent, possibly due to irritating effects of polluted air in the area.

A second group was made up of 74 patients who had what could be called chronic bronchitis. By history, the patients had had repeated infections in the past even before arriving in Japan. Previous pulmonary function studies were available on many of this group. If previous studies had not been available, this more severely ill group could well have been removed from the area and continue to show poor pulmonary function, which might erroneously be attributed to permanent ill effects of the so-called Tokyo-Yokohama asthma.

A third group, also comprising 74 patients, had a typical history of paroxysmal wheezing and coughing diagnostic of asthma. Their condition was often aggravated by going from Camp Zama to an area of high air pollution such as Yokohama. Forty per cent of this group had a history of asthma before coming to Japan. Seven of the 74 were evacuated from the area because of severe and persistent symptoms of asthma. None of the patients with acute bronchitis and only two of those with chronic bronchitis were evacuated. It is of special interest that 90 per cent of the asthmatic patients did not have severe disease and could be maintained in the area without resorting to heroic measures such as maintenance steroid therapy. Seventy-three per cent of this group had an "allergic background," defined as a past history of asthma, a family history of asthma or a past history of hay fever, urticaria or eczema. Fifty-four per cent of this group complained of severe nocturnal coughing as a major symptom. Most of them showed objective improvement in the one-second vital capacity after isoproterenol nebulization, and 8 per cent eventually had normal pulmonary function during the period of observation. In 47 per cent of them the proportion of eosinophiles exceeded 5 per cent. Almost all the patients who had illness severe enough to require evacuation from the area had an elevated eosinophile count suggesting an allergic basis for the disease.

As can be inferred from the foregoing, Spotnitz[10,11] believed that the asthma in this group is in no way different from perennial asthma seen anywhere, the only distinguishing feature being the obvious relationship between severity of symptoms and exposure to high levels of air pollution. Follow-up has revealed that many of these patients continue to have asthma after their return to the United States. Spotnitz concluded that Tokyo-Yokohama asthma is not a disease but a syndrome and that the majority of patients seeking medical attention for nocturnal wheezing and coughing had acute bronchitis, chronic bronchitis or asthma. It was his opinion that the high level of air pollution has an aggravating effect rather than a sensitizing role in the development of the asthmatic condition.

Discussion

For nearly 20 years now it has been suggested, and reports have supported the assumption, that Tokyo-Yokohama asthma is a distinct entity. The described clinical course of the patients has at times led physicians to conclude that there must be some sensitizing agent in the polluted atmosphere which in some way produces asthma in many foreigners coming into the area. However, rather thorough studies by the armed services, and more recently by Japanese investigators, have not disclosed such an etiologic agent. The Japanese are now finding the same increase of asthmatic conditions in their own people living in areas of high atmospheric pollution. Other areas throughout the world,[1,2,8,13] especially heavily industrialized ones, have had brief periods of unusually high concentration of air pollutants, associated with increased morbidity and mortality in patients with pulmonary disease. It has been experimentally shown in animals[4] that air pollutants irritate the respiratory tract and are conducive to the development and prolongation of acute respiratory infections. Both cigarette smoking and air pollution are given as distinct causes of chronic bronchitis in Great Britain.

Earlier reports suggested that there might be permanent residual damage if patients in whom asthma developed were not removed from this area. If substantiated, this would be of great military significance. However, Spotnitz[10,11] recently reported excellent data suggesting that Tokyo-Yokohama asthma is not a distinct clinical entity, but a clinical syndrome. In spite of all that has been reported in the past, it seems that Tokyo-Yokohama asthma is no different from asthma occurring anywhere in the world where there is heavy air pollution. Spotnitz's patients usually responded to the usual treatment for asthma and he felt that the disease was not of great significance from a military standpoint. This disease is of less military importance for the Air Force. From January 1964 to July 1964 only four patients were evacuated to the United States by the Air Force even though the Air Force population in Japan is much greater than the Army population there. This may be related to a screening program by the Air Force. Air Force military personnel and their dependents being assigned to an overseas area have their health records reviewed. It is usually advised that those with a history of asthma or chronic lung disease not be assigned to the Kanto Plain. My own observations during three years in Japan as a member of the Tri-Service Committee on Tokyo-Yokohama asthma and as Chief of Medicine at a large United States Air Force Hospital there, support Spotnitz's conclusions. I believe that the onset of cough and wheezing in the autumn and winter months just happens to coincide with the time of year that the incidence of respiratory infections is greatest. Nearly all the patients who have been reported are smokers and it is probable that this plus heavy air pollution irritates the respiratory tract, predisposing to infection or bronchospasm. Air pollution appears to have an aggravating effect rather than a causative effect in producing the symptoms of asthmatic type. At present research is continuing by the armed services and by Japanese investigators.

REFERENCES

1. Greenberg, L., Erhardt, C., Field, A. D., Reed, J. I., and Seriff, N. S.: Intermittent air pollution episode in New York City, 1962, Public Health Reports, 78:1061-64, December 1963.

2. Heinmann, Harry: Air pollution and respiratory disease, Annals of Allergy, 21:396-407, July 1963.

3. Huber, T. E., Joseph, S. W., Knoblock, E., Redfearn, P. L., and Karakawa, J. A.: New environmental respiratory disease (Yokohama asthma), A.M.A. Arch. Indust. Hyg. and Occupational Med., 10:399-408, November 1961.

4. Josephson, Alan S.: Immunologic methods in air pollution research, Arch of Environ. Health, 8:143-46, January 1964.

5. Phelps, Harvey W.: Pulmonary function studies used to evaluate air pollution asthma disability, Mil. Med., 126:282-86, April 1961.

6. Phelps, H. W., and Koike, S.: Tokyo-Yokohama asthma, Amer. Review of Resp. Dis., 86:55-63, July 1962.

7. Phelps, H. W., Sobel, G. W., and Fisher, N. E.: Air pollution asthma among military personnel in Japan, J.A.M.A., 175:990-993, 18 March 1961.

8. Oelsner, T., Massey, F., Portnoy, B., Wayne, W. S., Smith, K. R., and Wehrle, P. F.: Los Angeles air pollution and respiratory disease, Arch. of Environ. Health, 8:182-183, January 1964.

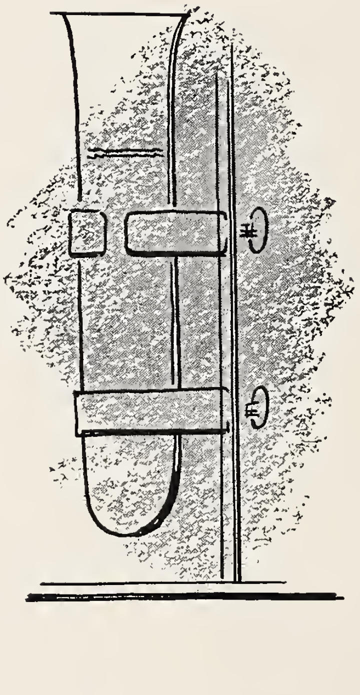
9. Smith, R. B. W., Kolb, E. J., Phelps, H. W., Weiss, H. A., and Hollinden, A. B.: Tokyo-Yokohama asthma, Arch. of Environ. Health, 8:805-817, June 1964.

10. Spotnitz, Murray: The significance of Yokohama asthma, Amer. Review of Resp. Dis., 92:371-75, September 1965.

11. Spotnitz, Murray: The effects of air pollution on military personnel in Japan, Annual Progress Report Pulmonary Lab. U.S. Army Med. Command, Japan, 1 July 1963-30 June 1964.

12. Toyama, Toshio: Air pollution and its health effects in Japan, Arch. of Environ. Health, 8:153-73, January 1964.

13. Weill, H., Ziskind, M. M., Derbes, V., Lewis, R., Horton, R. J. M., and McCaldin, R. O.: Further observations on New Orleans asthma, Arch. of Environ. Health, 8:184-87, January 1964.



Hemorrhagic Shock

Influence of Hyperbaric Oxygen on Metabolic Parameters

YORKE G. JACOBSON, M.D., *Pittsburg, California* • MELVIN KELLER, M.D., *Baltimore, Maryland*
ELDRED D. MUNDTH, M.D., *Boston, Massachusetts* • ALFRED J. DEFALCO, M.D., *Rochester, N.Y.*
JAMES E. MC CLENETHAN, M.D., *Washington, D.C.*

■ *Oxygen therapy at atmospheric and increased pressure was used in the treatment of experimental hemorrhagic shock. Arterial gases, pH, lactate and pyruvate were determined and compared. Survival was carefully followed and complete pathological evaluation was carried out. The results showed no difference between control animals and those in the hyperbaric oxygen therapy group. It was concluded that hyperbaric oxygen therapy* post facto *did not influence the metabolic or survival data in this experiment.*

THE BASIC MECHANISM in the pathophysiology of irreversible hemorrhagic shock is thought by some investigators to be defective tissue metabolite and gas exchange as a result of poor tissue perfusion in the post-hypotensive period. Theoretically, hyperbaric oxygen therapy (OHP) may be able to support the oxygen requirements of tissues struggling against an overwhelming burden of hypoxia. The ability of tissues to recover by extracting more oxygen than usual might extend the benefits of OHP to permit tissue survival at the extremely subnormal capillary blood flows which occur in the post-shock period.

In 1943 Frank and Fine[6] reported that three hours of OHP treatment during and after the induction of hemorrhagic shock in dogs did not change the survival rate from that of controls. They did not pursue their study further but concluded: "The course of events in hemorrhagic shock is in no way altered when venous anoxemia is prevented by administering oxygen at high pressure. Oxygen as a therapeutic agent in hemorrhagic shock is therefore of doubtful value."

More recently, however, Attar[1] and Elliott[5] reported an increased survival rate in dogs in hemorrhagic shock treated with oxygen at three atmospheres absolute* (3 AA) for two hours. In Attar's early study the OHP-treated dogs, however, were not continually bled to maintain a constant level of hypotension, and the control dogs did not appear to be in the same weight range as the treated animals. Furthermore, in neither of these studies was attempt made to simulate the clinical situation—that is, treatment of the shocked victim after replacement of the blood loss. The present study was therefore undertaken to evaluate oxygen therapy in a stage of shock considered irreversible because of the severity of the experimental preparation.

Method

New Zealand albino male rabbits weighing between 2.4 and 3.7 kg had splenectomy three weeks before the definitive experiment was begun. All

---

Department of Anesthesia, Sinai Hospital of Baltimore (Keller); first assistant resident in surgery, Massachusetts General Hospital (Mundth); associate in urology, Strong Memorial Hospital, and assistant in urology, University of Rochester School of Medicine (DeFalco); chief, thoracic surgery, Childrens Hospital (McClenethan).

This work was carried out at the Naval Medical Research Institute, Bethesda, Maryland. From the Bureau of Medicine and Surgery, Navy Department, Research Task No. MR 005.02-0020.01, Washington, D.C.

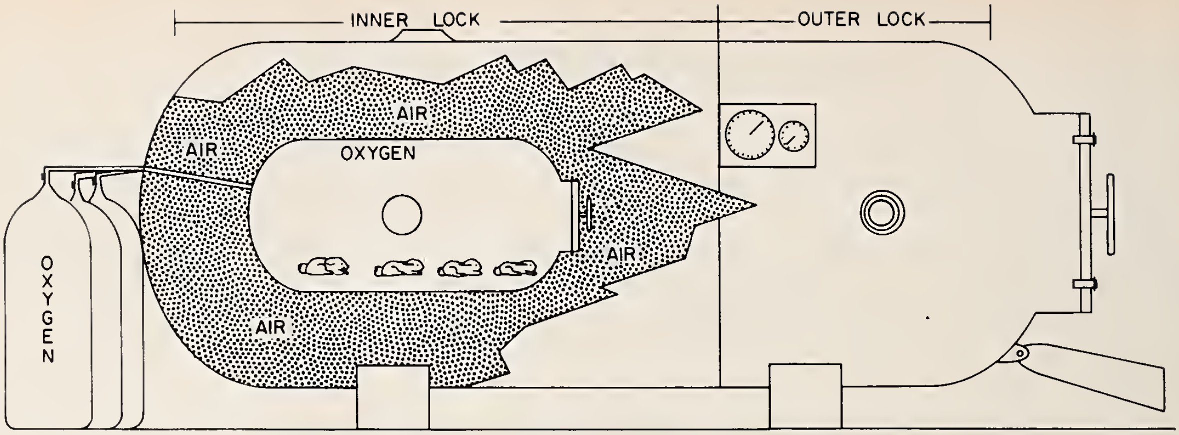
The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service-At-Large.

Read in part before the Surgical Forum at the American College of Surgeons Clinical Congress, 18 October 1965.

Submitted 18 March 1966.

Reprint requests to: 555 School Street, Pittsburg, California 94565 (Dr. Jacobson).

*Atmosphere Absolute (AA) is the pressure of the ambient air. Increases in pressure are designated by a number preceding the symbol AA; for example, 3 AA means three times the pressure of the ambient air.



EXPERIMENTAL PRESSURE CHAMBER NMRI, BETHESDA

Figure 1.—Hyperbaric facility at Naval Medical Research Institute.

animals had normal intestinal flora and were treated with penicillin and streptomycin during and after the experiment. Heparin was given before the induction of shock and at the time the shed blood was reinfused (2 mg per kg of body weight).

Using open drop ether and supplemental local anesthesia, the femoral artery was cannulated. When fully reactive the animals were bled into citrated Fenwal plastic bags in graded increments over a 15-minute period until a mean arterial pressure of 45 mm of mercury was recorded. This pressure was maintained by subsequent blood removal or replacement and sustained for five hours, during which time the animals were alert and responsive. At the end of five hours the shed blood was warmed to 37°C and was returned intra-arterially over a one-hour period. An additional 40 ml of citrated, cross-matched blood was given to replace that taken for samples. Random blood cultures were obtained to ensure that sepsis had not occurred during the shock period.

Three groups of animals were then studied:

Group I, 10 rabbits. After receiving their shed blood, these animals were kept in a constant temperature tank at 25°C, breathing room air, and were observed until death or survival occurred.

Group II, 10 rabbits. After receiving their shed blood, these animals were kept in a constant temperature tank at 25°C, breathing 100 per cent oxygen at ambient pressure (1 AA) for 36 hours or until death or survival was imminent. During sampling, however, they had to be removed to air.

Group III, 10 rabbits. These animals, having had all their blood returned, were placed in a standard Navy decompression chamber containing a smaller accessory tank, the former being compressed with air and the latter with oxygen. (See Figure 1.) They were kept at a constant temperature of 25°C at 2 AA, breathing 100 per cent oxygen, until death occurred or 12 hours of treatment completed. However, when samples were taken, the animals had to be removed from their oxygen environment to the larger chamber which was compressed with air at 2 AA. In Groups II and III, normal control animals (with spleen removed) were placed in the tanks with the experimental animals and were observed for signs of oxygen toxicity, which did not occur.

The oxygen concentration in the tanks was measured by gas chromatography and was maintained between 99 and 100 per cent. Arterial pH, oxygen and carbon dioxide (pO_2 and pCO_2) were measured on an Instrumentation Laboratory blood gas analysis apparatus and converted to the *in vivo* temperature by the nomogram of Severinghaus.[10] Arterial lactic acid was measured by the method of Barker and Summerson,[2] and pyruvic acid by Friedemann and Haugen's[7] technique. Base bicarbonate was determined from the Singer-Hastings[12] nomogram and converted to pH 7.4 to determine the bicarbonate deficit as described by Brown.[3] Excess lactate was determined by the formula of Sendroy.[9] Blood volumes were measured by use of radioactive iodinated serum albumin (RISA) and found to be about 8 per cent of the body weight. Blood samples were analyzed before shock, after two and a half hours of shock, after five hours of shock and then every three hours until death or survival occurred (up to 18 hours post-shock).

TABLE 1.—*Blood Gases*

	Baseline	*End of 5 Hr. Shock*	*3 Hr. Post-Bleed Reinfusion*	*6 Hr. Post-Bleed Reinfusion*	*9 Hr. Post-Bleed Reinfusion*
Air—					
pO_2 mm Hg	95±1.4	99±2.0	87±1.8	88±2.4	59±5.0
pCO_2 mm Hg	26.6±1.7	15.2±3.2	21.9±1.8	23.6±1.5	21.5±1.3
100 per cent O_2 surface—					
pO_2 mm Hg	96±1.8	88±1.2	79±1.2	81±1.4	68±1.2
pCO_2 mm Hg	27.2±1.0	15.5±1.2	18.4±1.4	20.1±1.3	19.6±1.1
100 per cent O_2 2 AA—					
pO_2 mm Hg	90±1.0	91±1.2	268±8.0	297±11.0	326±13.0
pCO_2 mm Hg	26.5±0.9	15.7±0.9	24.8±1.8	23.9±1.2	24.0±1.0

Survival over 48 hours was considered permanent. Autopsy was performed immediately on all animals that died.

Results

The amount of blood required for removal to produce shock varied between 27 and 38 ml per kg of body weight, and no significant difference was present in any group. Blood cultures showed no growth. Rectal temperature varied between 29°C and 31°C and no attempt was made to correct this. Several rabbits died during the shock period or while receiving their shed blood and were therefore not included.

Autopsy showed the following changes in all groups: *Liver*—central vacuolization and congestion with various degrees of necrosis. *Kidneys*—tubular vacuolization, congestion and focal necrosis with arteriovenous shunting, as evidenced by India ink and Fluorescin studies.[4] *Adrenals*—congestion and hemorrhage. *Heart*—congestion and focal areas of fibrosis and necrosis. *Small and large bowel*—congestion variable from moderate to severe with no necrosis. *Lungs*—almost all specimens had patchy atelectasis and congestion. *Brain*—only random study was made of this organ and no pathologic change was evident.

When statistical analysis of all the metabolic data was computed for unpaired specimens to a confidence limit of 95 per cent, there were no differences in any of the three groups when pCO_2 (Table 1), excess lactate (Table 2) and pH and bicarbonate deficit (Table 3) were determined. Survival time (Table 4) for Group I (air) was 11.6 ±0.7 hours and there were no survivors. Group II (oxygen-surface) survived 11.3±0.8 hours and there was one permanent survivor. Group III (oxygen—2 AA) survived 15.2±0.8 hours and there was one permanent survivor ($p<0.05$ compared with Groups I and II).

Discussion

The results of this study indicate from the parameters investigated that hyperbaric oxygen therapy (2 AA) instituted subsequent to a period of profound oligemic hypotension is ineffective in enhancing tissue oxygenation. This was evidenced by lack of reversal of the metabolic acidosis in the hyperbaric oxygen treated group compared with controls. A possible explanation for the failure of OHP to increase tissue oxygen extraction in the post-shock state is that tissue microcirculatory perfusion is greatly decreased and prevents the increased oxygen in solution to reach the tissues.

TABLE 2.—*Lactate, Pyruvate, and Excess Lactate Values*

	Baseline	*End of 5 Hr. Shock*	*3 Hr. Post-Bleed Reinfusion*	*6 Hr. Post-Bleed Reinfusion*	*9 Hr. Post-Bleed Reinfusion*
Air—					
Lactate mM/L	7.10±0.7	18.2±1.4	12.3±0.7	9.2±0.8	7.2±0.6
Pyruvate mM/L	0.35±0.03	0.49±0.03	0.47±0.03	0.45±0.04	0.40±0.05
Excess Lactate	....	6.4±0.6	1.7±0.4	....	....
100 per cent O_2 surface—					
Lactate mM/L	6.90±1.0	16.7±1.6	13.7±1.3	8.9±1.1	8.2±1.0
Pyruvate mM/L	0.4±0.04	0.49±0.03	0.48±0.04	0.43±0.07	0.37±0.04
Excess Lactate	....	6.4±0.8	2.8±0.2	....	....
100 per cent O_2 2 AA—					
Lactate mM/L	6.40±0.6	17.6±1.4	12.1±1.4	10.0±1.2	7.8±1.1
Pyruvate mM/L	0.36±0.03	0.55±0.02	0.41±0.03	0.38±0.03	0.32±0.03
Excess Lactate	....	6.9±0.9	1.9±0.3	....	....

TABLE 3.—*Bicarbonate Values Corrected to pH 7.4, Bicarbonate Deficit, and pH*

	Baseline	*End of 5 Hr. Shock*	*3 Hr. Post-Bleed Reinfusion*	*6 Hr. Post-Bleed Reinfusion*	*9 Hr. Post-Bleed Reinfusion*
Air—					
HCO_3 (pH 7.4) meq/L	14.9±1.5	4.5±1.1	10.5±1.5	12.2±1.8	12.2±2.1
HCO_3 Deficit	....	10.4±1.8	4.60±1.5	3.30±1.6	3.70±0.8
pH	7.37±0.01	7.12±0.04	7.34±0.03	7.36±0.03	7.40±0.04
100 per cent O_2 surface—					
HCO_3 (pH 7.4) meq/L	15.1±1.3	5.6±0.5	9.0±1.1	11.0±1.1	11.6±0.8
HCO_3 Deficit	....	10.5±1.7	6.7±0.9	5.1±1.1	2.8±0.4
pH	7.40±0.01	7.30±0.05	7.32±0.06	7.34±0.06	7.36±0.09
100 per cent O_2 2 AA—					
HCO_3 (pH 7.4) meq/L	15.4±1.3	5.1±0.7	10.2±1.4	10.3±1.4	12.2±1.1
HCO_3 Deficit	....	12.3±1.8	6.3±1.7	4.2±1.6	2.5±1.0
pH	7.45±0.01	7.24±0.04	7.32±0.03	7.32±0.05	7.35±0.03

Schumer,[8] Shoemaker[11] and others have suggested that the tissue microcirculatory perfusion changes develop during the period of hypotension and persist even after the blood volume is replaced. This could explain the observation of Attar, Elliott and others that hyperbaric oxygen improves survival at the initiation and during oligemic shock. In these situations the increased tissue oxygenation provided by OHP in the basal state and early in the hypotensive period may well improve survival from hemorrhagic shock.

Although tissue pO_2 tension was not measured in this study, it would be of great interest to do so under the different experimental conditions whereby tissue oxygen tensions could be quantitatively assessed and the efficacy of hyperbaric oxygen ascertained more directly. Similarly, it would be of considerable interest to measure cardiac output which is known to be reduced in oligemic shock and in the post-reinfusion period to ascertain any effect hyperbaric oxygen might have on this.

We would conclude from this study that altered circulatory dynamics are the primary pathophysiologic mechanism in hemorrhagic shock and that hyperbaric oxygen administered *post facto* is ineffective in reversing the severe metabolic changes associated with hemorrhagic shock.

TABLE 4.—*Survival Time*

	Mortality Rate (Per Cent)	*Survival Time (hours)*
Air	100	11.6±0.7
100 per cent O_2 surface	90	11.3±0.8
100 per cent O_2 2 AA	90	15.2±0.8
		$p<0.05$

REFERENCES

1. Attar, S., Esmond, W. G., and Cowley, R. A.: Hyperbaric oxygenation in vascular collapse, J. Thor. & Cardiovasc. Surg., 44:759, 1962.

2. Barker, S. B., and Summerson, W. H.: The colorimetric determination of lactic acid in the biological material, J. Biol. Chem., 138:535, 1941.

3. Brown, E. B.: Plasma electrolyte composition in dogs breathing high CO_2 mixtures, Report 57-115, Air University School of Aviation Medicine, USAF, Randolph AFB, Texas, 1957.

4. Defalco, A. J., Mundth, E. D., and Beckman, E. L.: Renal hemodynamics following renal artery occlusion: The importance of renal venous pressure, Fed. Proc., 23:487, 1964.

5. Elliott, D. P., and Paton, B. C.: Effect of 100 per cent oxygen at 1 and 3 atmospheres on dogs subjected to hemorrhagic hypotension, Surgery, 57:401, 1965.

6. Frank, H. A., and Fine, J.: Traumatic shock: A study of the effect of oxygen on hemorrhagic shock, J. Clin. Invest., 22:305, 1943.

7. Friedemann, T. E., and Haugen, G. E.: Determination of keto acids in blood and urine, J. Biol. Chem., 147:415, 1943.

8. Schumer, W.: Study of the effects of norepinephrine on the microcirculation of the dog omentum in oligemic shock, Surg. For., XIV:19, 1962.

9. Sendroy, J.: Relationship of oxygen debt to blood lactate and pyruvate in exercised dogs, Research Report Project NM 004.006.0401, Naval Medical Research Institute, 1958.

10. Severinghaus, J. W.: Oxyhemaglobin dissociation curve correction for temperature, J. Appl. Physiol., 12: 485, 1958.

11. Shoemaker, W. C.: Studies in viscosity alterations in shock, Arch. Surg., 85:492, 1962.

12. Singer, R. B., and Hastings, B.: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood, Medicine, 27:223, 1948.

Hyperbaric Oxygen in Therapy of Gas Gangrene

Report of a Case Following Induced Abortion

KARL L. SCHAUPP, JR., M.D., DOUGLAS PINTO, M.D., AND
RODNEY J. VALENTINE, M.D., *San Francisco*

■ *The treatment of gas gangrene has been revolutionized by oxygen drenching of tissues infected with Clostridia. This was used in a massive infection of the abdominal wall following a traumatic abortion attempt. The clostridial infection was controlled, but the patient almost succumbed to a secondary infection of gram-negative organisms. This responded to drainage, antibiotics and general supportive measures. In the course of treatment, the value of a team approach to complicated special problems was documented.*

AS RECENTLY AS 1962 acute, progressive infection with *Clostridium perfringens* (welchii) was considered inevitably fatal unless the infected tissue was completely removed, regardless of what auxiliary therapeutic agents were used or in what amounts they were administered.[7] The organism is a spore-bearing obligatory anaerobic bacillus which produces a number of toxins which are exo-enzymes. The bacillus itself is of a saprophytic nature and it is the toxin production which creates its micro-environment and makes it lethal. Anaerobic conditions, necrotic tissue, poor blood supply and foreign bodies are factors that contribute to an environment favorable for aggressive reproduction of the organism.

The mere presence of the bacillus is not proof of infection. MacLennan[7] described three clinical situations from which the organism could be recovered: Simple contamination without infection, anaerobic cellulitis and anaerobic myonecrosis. Only the latter is considered true gas gangrene. A high proportion (27 per cent) of women in a state of abortion have *Cl. perfringens* in high vaginal swabs.[9] The organism is universally present in the bowel and in 8 to 10 per cent of normal vaginas, but it is an incidental finding in cases other than those with myonecrosis.

Surgical excision of infected tissue has been the mainstay of treatment to present times. In wounds, this means amputation of limbs and extensive mutilating operation. In the uterus, hysterectomy has been lifesaving. Kadner and Anderson[6] reviewed the reported cases since 1950 and added seven more in 1963. Some of these were not unequivocal cases of myonecrosis. In 1965 Browne[2] reported two cases which followed cesarean section. Hysterectomy was lifesaving.

In 1961 Brummelkamp[3] reported experimental evidence and three cases showing the value of drenching the tissues with oxygen. This was done by having the patient breathe 100 per cent oxygen under a pressure of three atmospheres (absolute) for two hours with five to seven sessions in three days. The hemoglobin saturation is not changed by this, but the amount dissolved physically in the plasma is increased 15 times. The oxygen available in this solution finds its way into the infected area and interferes with the metabolic processes of the anaerobic *Cl. perfringens*. This stops the toxin production which is necessary to maintain the micro-environment of the organism. It does not kill the organism, and living bacilli have been recovered from clinically healed deep wounds.[4] Smith[8] reported three cases in 1962, but considered the oxygen therapy only as an aid to the usual surgical measures and to administration of penicillin and antitoxin. Boerma,[1] taking note of

---

Chairman's address: Presented before the Section on Obstetrics & Gynecology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 490 Post Street, San Francisco, California 94102 (Dr. Schaupp).

Smith's report, said that oxygen drenching was lifesaving, permitting conservatism in surgical measures and saving extremities from amputation. Jackson[5] in 1965 reported a case of abdominal wall infection following bowel resection. In spite of heroic measures, the infection progressed beyond surgical reach and the patient was apparently doomed until hyperbaric oxygen was remembered and appropriate treatment effected a cure. It is interesting to note that Browne's cases[2] were presented in late 1965 and no mention was made of oxygen therapy.

Report of a Case

In the afternoon of 30 December 1964 a 27-year-old white woman, para 2, was admitted to hospital with a diagnosis of acute pelvic inflammatory disease following an abortion 36 hours previously. The patient was far sicker than expected, and the passage of a foul-smelling macerated fetus about 18 cm long prompted a review of what had happened. With mistaken dates in mind (last menstrual period 15 November 1964) the patient had been aborted by someone not aware of the existence of a twin. The procedure had taken two hours and was obviously traumatic. A pack was inserted and the patient sent home. The pack had been removed in 12 hours.

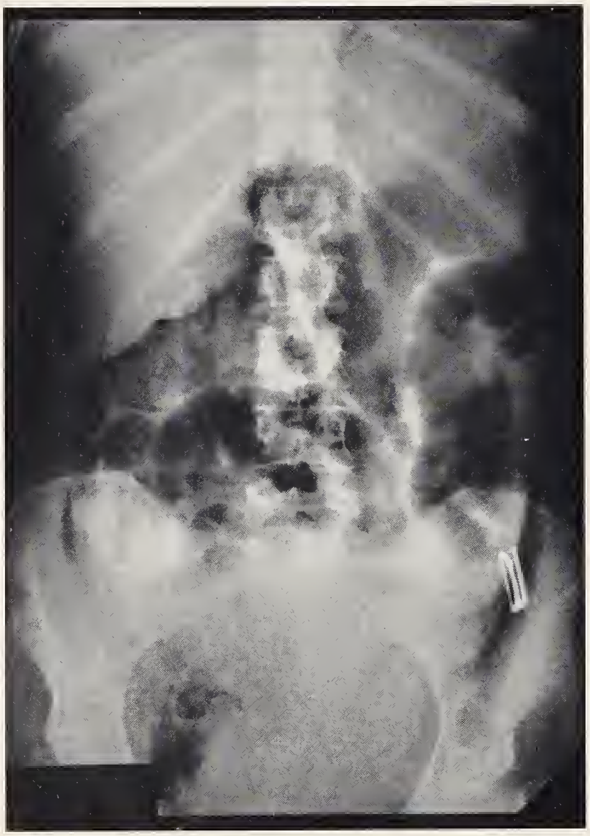


Figure 1.—Film of abdomen on admission. Note extraperitoneal gas under metal clip and in corresponding area on the right. Also, foamy mass in pelvis.

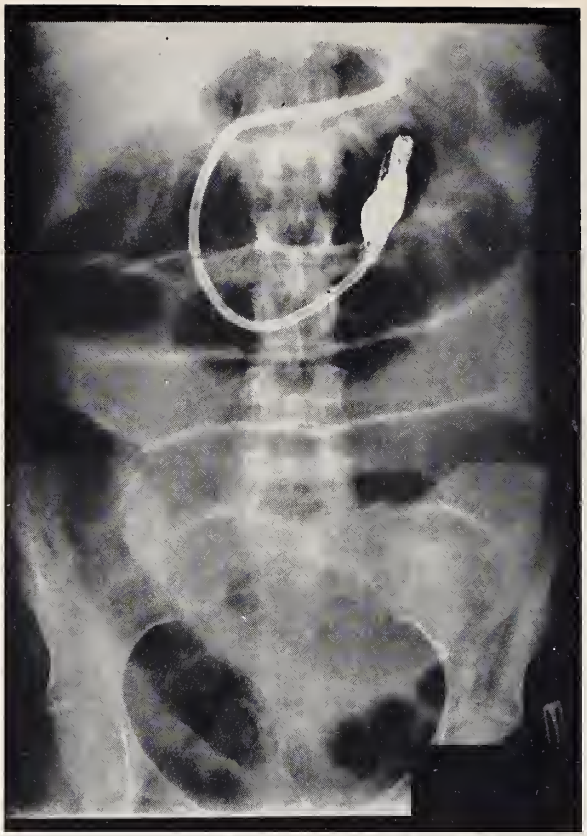


Figure 2.—Massive distension on third day. Note long tube in duodenum. Extraperitoneal gas still present.

On physical examination the patient appeared extremely ill. The temperature was 37.6°C (99.7°F), pulse 120, respiration 18 and blood pressure 105/50 mm of mercury. The abdominal wall was rigid and there was a bronze discoloration of the lower abdomen. There was decided abdominal tenderness and no bowel sounds. The cervix was open and showed ecchymosis on the anterior lip. A culture was taken from the cervical discharge. The blood showed a hemoglobin of 9.9 gm per 100 ml and packed cell volume of 30 per cent. Leukocytes numbered 18,100 per cu mm. Upright and decubitus x-ray films showed gas in tissue planes of the lower abdomen and a foamy mass in the pelvis (Figure 1).

Administration of fluids by vein and of penicillin and streptomycin was begun. In a few hours, the culture confirmed the source of the gas in the tissues as *Cl. perfringens* and the patient was promptly transferred to Presbyterian Medical Center for hyperbaric oxygen therapy. The urinary output was low and the patient had hypotension. She was placed in the oxygen chamber at 11:45 a.m. and given 50 minutes of 100 per cent oxygen at three atmospheres (absolute) of pressure. An intravenous cutdown was placed to manage fluid and electrolyte balance. A Foley catheter and a nasogastric tube were inserted. Penicillin G, to which the organism was sensitive, was given in a dose of 60 million units daily in the intravenous fluids. Streptomycin, 0.5 gm intramuscularly twice daily, was also given. The oxygen therapy was repeated at 9:30 p.m. At 11:30 p.m. the patient passed a foul-smelling placenta 8×10×2 cm. Cultures from it contained *Cl. perfringens.*

The following day the oxygen therapy was repeated twice. The uterus was explored with the patient in bed and only a few small fragments of tissue and 30 ml of straw-colored fluid were recovered. Two units of whole blood were given with continuing fluid and electrolyte balance. The plasma hemoglobin was 14 mg per 100 ml and the urinary hemoglobin 1.3 mg, indicating hemolysis. The abdomen was distended and the patient was disoriented. On the third day the same regimen was continued (without oxygen therapy) but pronounced distension raised the question of mechanical bowel obstruction (Figure 2). Placement of a long tube helped improve the condition and the patient passed some flatus. The temperature and pulse rate were down (Chart 1). On the fourth day the patient was improved, but the following day jaundice was noted and a sudden rise in temperature to 38.9°C (102°F) occurred in the evening (Chart 1). Two units of whole blood were included in the fluids.

On the sixth day it was thought there was an increase in the extraperitoneal gas as seen roentgenographically. As this was considered due to a reactivation of the *Cl. perfringens,* hyperbaric oxygen therapy was begun again. Because there was no response, colymycin and methicillin were given in the next two days. Streptomycin was discontinued. Three units of blood were used.

On the ninth day the patient was in critical condition. There was low output of urine and she was hypotensive. On aspiration in the right lower quadrant of the abdomen, a tan fluid was withdrawn which showed gram-negative rods on stain-

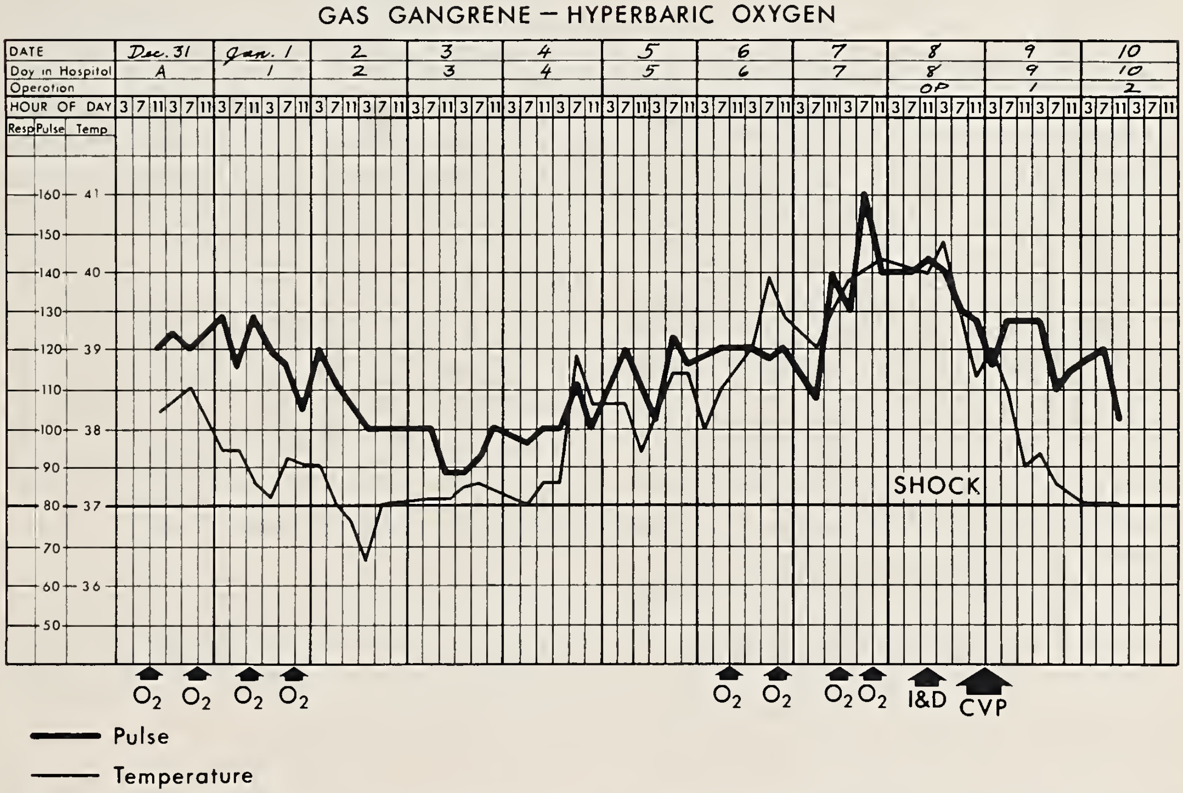


Chart 1.—Graphic record of critical times in the course of the infection. O_2=hyperbaric oxygen. I & D=incision and drainage. CVP=central venous pressure.

ing. Cultures showed *E. coli* and *Bacteroides*. With this evidence the patient was taken to the operating room and a large incision made down to the preperitoneal space in each lower quadrant. The peritoneum was surrounded by a foul-smelling abscess cavity as far up as the umbilicus and down into the pelvis. The levator on the right was found perforated, with a tract leading to a bulla on the right lateral perineal area. This was incised. Necrotic tissue was removed from the incision on the right. The patient was in shock. She received seven units of whole blood, some of it under pressure. A central venous pressure catheter was placed through the right external jugular vein to monitor the amount of blood needed. Penicillin was discontinued and chloramphenicol started at a dose of 500 mg intramuscularly every six hours. The next day the temperature and the pulse rate fell dramatically (Chart 1). The urine output was only 150 ml in 24 hours. Blood clotting was poor and calcium gluconate was given intravenously. The patient was jaundiced. One unit of blood was given and another the next day. Urine output increased and diuresis occurred on the 12th day. Jaundice was decreasing. Fluids by mouth were started on the 13th day and food intake was increased to a regular diet with beginning ambulation in the next few days.

On the 15th day the antibacterial action of the patient's serum against E. coli cultured from the uterus was 1:8. On the day before the test, she had received 60 million units of penicillin, 300 mg of colymycin and 500 mg of chloramphenicol. The chloramphenicol was discontinued the next day.

Seventeenth day: A small infra-umbilical incision was made into a small abscess. Irrigations were begun with 500 mg of neomycin in 1,000 ml of normal saline solution. The irrigation solution would flow from the upper incision to the inguinal incisions and through to the drainage wound in the right perineal area. The foul-smelling drainage improved immediately.

Twenty-second day: Penicillin G was started in a dose of 600,000 units intramuscularly every eight hours. Benemid, 0.5 gm, was given by mouth with each dose. This was continued for 10 days along with the irrigations, and the temperature gradually decreased to normal. The wounds cleared and granulations formed. The patient was dismissed 10 February 1965 with a Foley catheter in the bladder, as she could not void.

She was examined occasionally as an outpatient. Some bladder tone returned and the Foley tube was removed. At last report the wounds were healed but there was some loss of tone of the abdominal muscles, although they functioned adequately. The bladder and bowel were hypnotic, but functioned with special attention. Apparently menses appeared three to four months after dismissal. After menstruation was late in one cycle, sequential hormonal therapy was begun. This has not produced further bleeding. The patient is functioning normally and is working at her former job as a receptionist.

Discussion

The problems presented in this case needed the special knowledge and techniques of experts in general surgery, internal medicine, bacteriology and gynecology. As in many other areas of medicine, the team approach was the only rational way to offer a desperately ill patient the best chance for survival. One of the main aims of modern practitioners of medicine should be to know generally what current scientific advances have been made, and then make them available to the patient. This means calling specially qualified consultants in time.

To summarize briefly, the patient had an overwhelming infection with *Cl. perfringens* which responded dramatically to hyperbaric oxygen therapy. A second wave of Gram-negative invaders then took over the abscess cavity which was ideal for their propagation. This caused shock, anuria, hemolysis and jaundice. Administration of antibiotics, hyperbaric oxygen, fluid and blood and maintenance of electrolyte balance barely kept the patient alive until the cavity was incised and drained. This was the second critical turning point and the patient then began to recover.

The problem of one infection following the other is common in gas gangrene, as the infections are mixed. Oxygen drenching should be used as soon as possible, but adequate debridement and drainage along with appropriate antibiotics and general support are also of utmost importance.

ADDENDUM: The patient was seen at Presbyterian Medical Center in the spring of 1966 for cosmetic revision of scars from the previous procedures. The organs, viewed through a reopened incision in the right inguinal area, appeared normal. The patient still had not menstruated since the time of the last previous observation, but she was contemplating marriage.

REFERENCES

1. Boerma, I., and Brummelkamp, W. H.: Inhalation of oxygen at two atmospheres for Cl. welchii infections, Lancet, 2:990, 10 November 1961.

2. Browne, J. T., Van Derhor, A. H., McConnell, T. S., and Wiggins, J. W.: Cl. perfringens myometritis complication cesarean section, a report of two cases. Presented at District VIII ACOG meeting in Las Vegas, 25 October 1965. To be published.

3. Brummelkamp, W. H., Hogendijk, J., and Boerma, I.: Treatment of anaerobic infections (clostridial myositis) by drenching the tissues with oxygen under high atmospheric pressure, Surgery, 49:299-302, March 1961.

4. Brummelkamp, W. H.: Considerations on hyperbaric oxygen therapy at three atmospheres absolute for clostridial infection type welchii, Annals of the New York Academy of Sciences, 117, Article 2:688-699, 21 January 1965.

5. Jackson, D. R.: Hyperbaric oxygenation in treatment of gas gangrene, J.A.M.A., 193, No. 5:395-396, 2 August 1965.

6. Kadner, M., and Anderson, G.: Septic abortion with hemoglobinuria and renal insufficiency with special reference to Cl. welchii infection, Obstetrics and Gynecology, 21, No. 1:86-94, 1 January 1963.

7. MacLennan, J. D.: The histotoxic clostridial infections of man, Bacterial. Rev., 26:177-274, June 1962.

8. Smith, G., Siller, W., Norman, J. N., Ledingham, I. McA., Bates, E. H., and Scott, A. C.: Inhalation of oxygen at two atmospheres for Cl. welchii infections, Lancet, 2:756, 13 October 1962.

9. Smith, K., Browne, J. C., Shackman, R., and Wrong, O. M.: Acute renal failure of obstetric origin, Lancet, 2:351-354, 21 August 1965.

The Neck Venous Hum in Adults

ARTHUR U. RIVIN, M.D., *Los Angeles*

■ *In a survey of 200 persons, ages 18 to 76, the incidence of normal cervical venous hum was 47 per cent in young adults and 21 per cent in persons of middle and older age, a group in whom it once was thought to be rare. The importance of the hum is that it may be misinterpreted as caused by a pathologic state such as an arteriovenous aneurysm, aortic insufficiency, carotid artery stenosis, patent ductus arteriosus or thyrotoxicosis.*

The normal cervical venous hum may be distinguished clinically from murmurs associated with disease states by the fact that it can be silenced by light pressure over the jugular vein.

NOW THAT PHYSICIANS are more often applying the stethoscope to the neck to detect carotid artery stenosis, an odd murmur that is sometimes heard just above the clavicle has perplexed some examiners. The strange sound is a normal venous hum, known to be common in childhood[3] but until the reports by Jones[2] and by Allen and Mustian,[1] thought to be infrequent in adults. I write this report to call attention to the possibility of misinterpretation of this sound and to emphasize that it is common in adults.

Materials and Methods

Two hundred adult patients of two general age groups were examined. A young adult group was made up of 45 men and 39 women, ages 18 through 25, who were seen in the cardiology clinic of a university health service. A middle age and older age group was composed of 48 men and 68 women, ranging in age from 26 to 76, who were seen in the private practice of internal medicine.

Patients were examined with the stethoscope while in the upright and recumbent positions, and with the breath held. Moderate pressure with the bell was often necessary to elicit the murmur.

Location and Characteristics

The hum was best heard just above the clavicle and lateral to the clavicular head of the sternocleidomastoid or between the lateral and medial sternocleidomastoid heads. Most commonly it was heard only on the right side, but often on both sides, and in two persons on the left only. Although the murmur was usually heard only in the prime area, in 10 instances it was heard all over the supraclavicular fossa, up to the angle of the jaw or into the upper chest. It varied from a loud to and fro roar, to a musical "whee," to a faint, low-pitched hum with a long diastolic component. Characteristically, it disappeared on pressure over the external or anterior jugular vein or when the patient reclined. No special features of chest or neck contour distinguished the patients in whom the hum was heard, nor was there evidence of any disease state associated with the hum.

Frequency

The hum was heard in 24 of the patients in the group of 116 over the age of 25, an incidence of 21 per cent. Eight of these patients were over 50

From the Student Health Service and the School of Medicine, University of California, Los Angeles.

Submitted 10 February 1966.

Reprint requests to: 10921 Wilshire Boulevard, Los Angeles, California 90024.

years of age. It was heard in 40 of the 86 in the young adult group, an incidence of 47 per cent. The incidence was about the same in women as in men.

Diagnostic Errors

Perhaps of greatest interest is the mistaking of a normal venous for a significant abnormality. The following clinical summaries illustrate the possible errors:

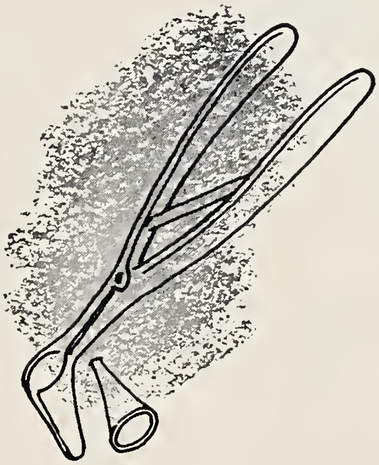
- In a woman 72 years of age with symptoms of intermittent cerebral ischemia, venous hum was interpreted as caused by carotid artery stenosis.
- In a 44-year-old man who had myocardial infarction, a prominent long, low diastolic component of the hum, well heard in the aortic area, was misinterpreted as due to aortic insufficiency.
- Venous hum in a 45-year-old woman with prominent goiter with hyperthyroidism, was thought to be bruit of thyroid vessels in thyrotoxicosis.
- A loud to and fro hum over the upper sternum in a 21-year-old man was thought to be caused by patent ductus arteriosus.
- A very loud continuous roaring hum at the base of neck of a 60-year-old man was misdiagnosed as arteriovenous aneurysm.

REFERENCES

1. Allen, N., and Mustian, V.: Origin and significance of vascular murmurs of the head and neck, Medicine, 41:227-47, September 1963.

2. Jones, E. L.: Frequency, characteristics and importance of cervical venous hum in adults, N. Engl. J. Med., 267:658-60, 27 September 1962.

3. Levine, S. A., and Harvey, W. P.: Clinical Auscultation of the Heart, W. B. Saunders Co., Philadelphia, 1949, p. 272.



Achondroplastic Dwarfism

Effects of Treatment With Human Growth Hormone

ROBERTO F. ESCAMILLA, M.D., JOHN J. HUTCHINGS, M.D.
CHOH HAO LI, PH.D., AND PETER FORSHAM, M.D., *San Francisco*

■ *Two male patients with achondroplastic dwarfism aged 7-5/12 and 14½ years were treated with human growth hormone 5 mg daily. Both showed nitrogen retention on balance studies, the older second patient to a marked degree. In the younger patient, height increased from 95.4 to 106.3 cm on* HGH *5 mg daily alone for 14 out of 24 months. The rate of growth approximately doubled during the first two treatment periods as compared with the pre-treatment rate. In the second older patient* HGH *was administered 5 mg daily intramuscularly for 21 out of 33 months. Growth from 129.6 cm to 137.8 cm occurred with the rate increasing following the addition of Na-l-thyroxine to the routine. This increased growth rate occurred during the post-puberty deceleration phase. Bone ages, interpreted from changes in the phalanges and metacarpals, increased from 4½ to 6 years during 16 months in Case 1, and from 13½ to 18 years in 33 months in Case 2. Transient adolescent gynecomastia appeared in Case 2. No local or general toxic effects were noted.*

These results are suggestive, but whether or not the eventual height of an achondroplastic dwarf can be significantly altered must await further studies.

METABOLIC AND GROWTH-STIMULATING effects of human growth hormone (HGH) in pituitary dwarfism have been previously reported.[3,6] Encouraging results in another type of dwarfism, gonadal dysgenesis (Turner's syndrome), in which pituitary deficiency is presumed not to be present, have also been noted.[4,7] In this communication we present the results of trials in two patients with achondroplasia, another condition in which the pituitary function is considered to be normal, with the typical short stature resulting from abnormal skeletal development.

Plan of Study and Methods

Both patients were examined at the San Francisco Medical Center of the University of California. Constant intake studies and frequent serum chemical studies, endocrine function tests and x-ray examinations were carried out by methods previously described.[6,7]

The human growth hormone administered was prepared by Dr. C. H. Li in the Hormone Research Laboratory by methods previously described.[8]*

From the Departments of Medicine and Pediatrics and the Metabolic Research Unit, University of California School of Medicine, San Francisco, and the Hormone Research Laboratory, University of California, Berkeley.

Supported in part by Grant No. A3870 from the National Institutes of Arthritis and Metabolic Disease, United States Public Health Service. Also supported in part by the E. C. Fleischner Fund through the Department of Pediatrics and the Morris Herzstein Fund, University of California School of Medicine, San Francisco.

Submitted 8 April 1966.

Reprint requests to: Department of Medicine, U.C. Medical Center, San Francisco, California 94122 (Dr. Escamilla).

*Work supported in part by a Grant from the American Cancer Society.

The pituitary glands used were obtained from human autopsy material with the help and cooperation of many persons. Collection of the glands was aided by the Pituitary Bank of the University of California School of Medicine[†] and by the Pituitary Bank Foundation.

TABLE 1.—*Laboratory Findings in Case 1 (April 1962, unless otherwise dated)*

Protein-bound iodine—5.9 mcg per 100 ml
BEI—5.3 mcg per 100 ml
Serum cholesterol—221 mg per 100 ml; on 25 August 1963, 161 mg
Serum phosphorus—4.4 mg per 100 ml; in November 1962, 5.3 mg
Serum alkaline phosphatase—6.4 Bodansky Units
Blood urea nitrogen—12.8 mg per 100 ml
Urinary 17 ketosteroids—0.4 mg per 24 hours
Urinary 17 hydroxycorticoids—2.4 mg per 24 hours
Urine gonadotropins—±2.5 mouse uterine units; on 26 August 1963, negative at 5 units

Glucose Tolerance Test Results (in mg per 100 ml)

	April 1962	*November 1962*	*August 1963*
Fasting	97	68	71
Postprandial			
½ hour	127	112	125
1 hour	103	94	70
1½ hours	98	92	......
2 hours	129	75	77
3 hours	......	......	68
4 hours	......	......	77

Intelligence quotient: 99.

Reports of Cases

CASE 1.—The patient, a boy, was admitted for examination and study 5 April 1962 when aged seven years and five months. The diagnosis of achondroplasia had been made at three weeks of age. Both parents were of normal height and there was no family history of dwarfism. The patient's

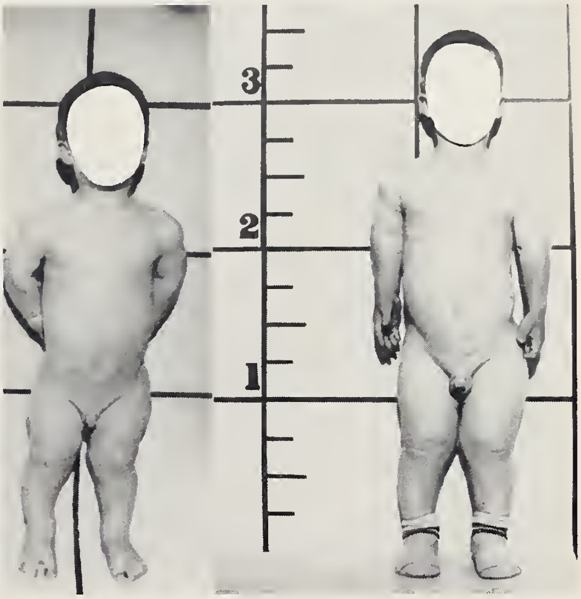


Figure 1.—Patient in Case 1. *Left*, height at 7 years 5 months of age, 95.4 cm. *Right*, 8 years 6 months, height 101.2 cm.

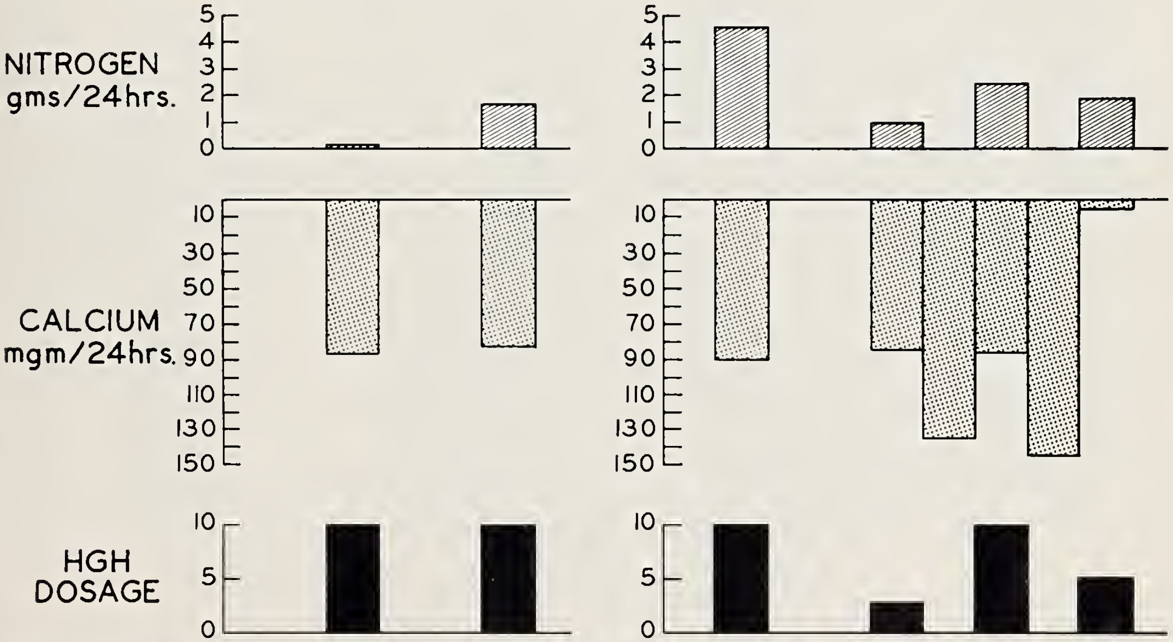


Chart 1.—Effects of HGH on urinary nitrogen and calcium in two boys with achondroplasia. Chart at left shows effects in Case 1, that at right the effects in Case 2. (HGH = human growth hormone.)

[†] Aided by Grants from the Jefferson McLeod Moore Fund.

general health had been good, and no previous treatment had been administered to attempt stimulation of rate of growth. In the preceding two years he had grown approximately 4.5 cm (1¾ inches) each year.

On examination his height was 95.4 cm (37⅝ inches) compared with a normal mean for his age of 127 cm (50 inches). He weighed 19.5 kg (43 pounds). The appearance and build were typical of achondroplastic dwarfism (Figure 1). Bone age was estimated at 4½ years.‡ Other laboratory findings are shown in Table 1. During constant intake, administration of 10 mg of HGH daily for a six-day period showed little retention of nitrogen over a baseline, but calcium diuresis averaging 84 mg daily occurred (Chart 1). Treatment with HGH, 5 mg daily intramuscularly, was started on 17 April 1962. The intermittent treatment schedule and subsequent heights and bone ages are listed below and also are shown graphically in Chart 2.

Case 2.—A boy 14 years and one month of age, in whom a diagnosis of achondroplasia had been confirmed at age seven months, was admitted 8 July 1961. No other instances of the condition were known in the family. The mother and father were of short normal stature, and a younger

Date	*Treatment*	*Height (cm)*	*Bone Age (years)*
17 April 1962 (age 7 yr. 5 mo.)	HGH 5 mg a day	95.4	4½
25 July 1962	Discontinue HGH	97.7	4½
13 November 1962*	HGH 5 mg a day	98.4	4½
23 February 1963	Discontinue HGH	100.6	5
8 May 1963	None	101.2	
30 August 1963	Resume HGH 5 mg a day	102.6	6
28 October 1963	Same—occasionally missed	103.0	
13 February 1964	Same—missed 4-5 days	104.6	
16 March 1964	Same—missed 7 days	105.0	
13 May 1964	Same—missed 7 days	106.3	
June 1964	Family moved—contact lost		

*Constant intake study with 10 mg HGH for 6 days showed average daily nitrogen retention of 1.6 gm, and average calcium diuresis of 82 mg.

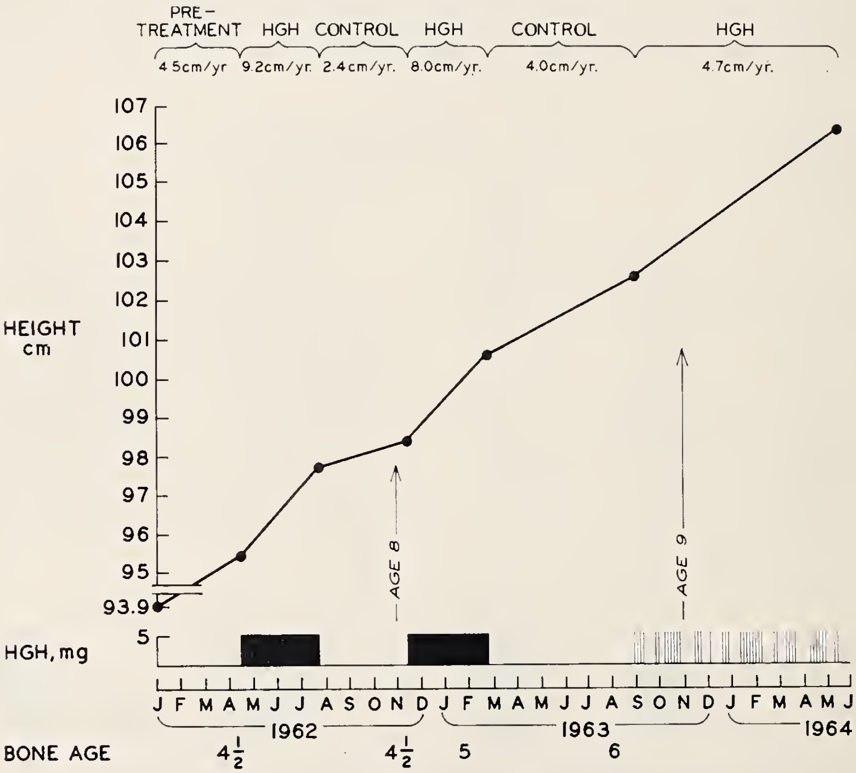


Chart 2.—(Case 1) Linear growth response to HGH in achondroplasia.

---

‡We are grateful to Dr. Howard Steinbach for these interpretations. Films of the hand and wrist were used. Comparison with Greulich and Pyle standards was difficult because of distortion of the joints, and estimations were based largely on the appearance of the phalanges and metacarpals, which were considered more reliable.

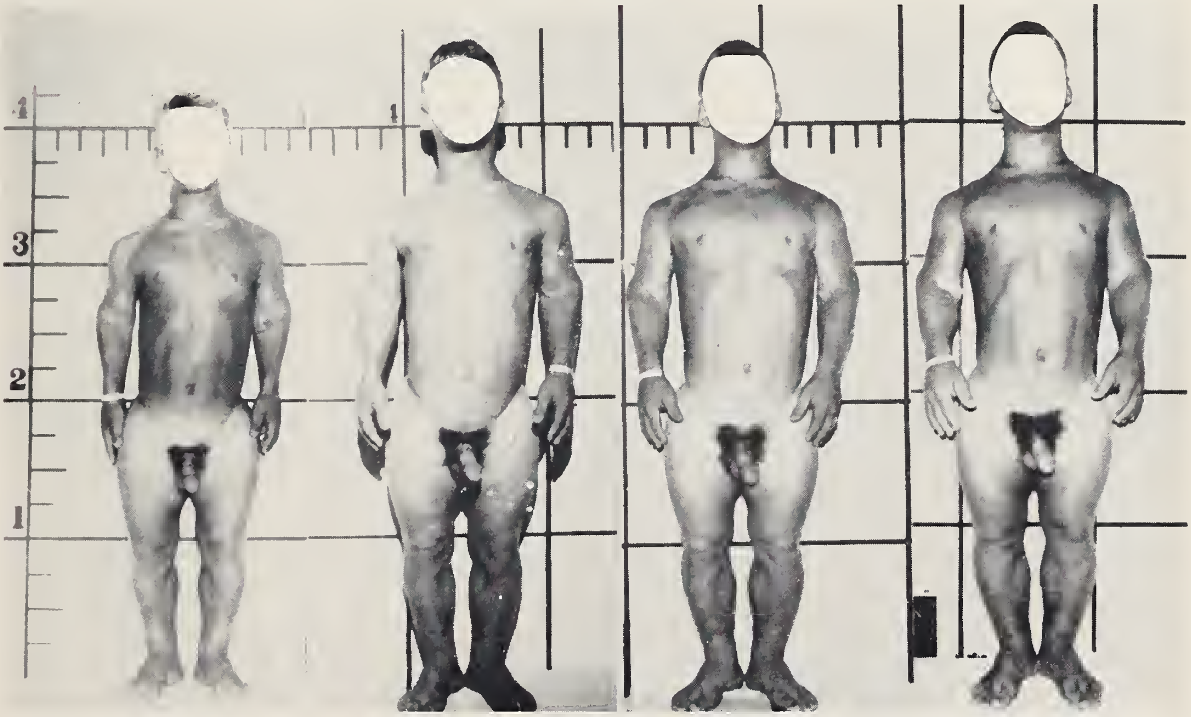
brother and sister were normal though rather short, conforming to the family pattern.

Various treatments for stimulation of growth had been tried in the past—all without definite effect. These treatments included vitamin B_{12} when the patient was three years old, methyltestosterone and terramycin when aged four, insertion of ivory pegs at the elbows and knees to attempt epiphyseal stimulation when aged five, Orexin® (vitamin B_1, B_6, and B_{12}) with aureomycin for one year when aged eight, and human chorionic gonadotropin (Antuitrin S®) intramuscularly with thyroid orally for two months when aged nine. When aged 11 short metabolic balance studies had been performed with HGH prepared by both the Raben[10] and Li[8] methods, and also with chymotrypsinized beef growth hormone[9] and sheep prolactin.[1] All of these studies had shown only equivocal effects during studies of nitrogen balance, so no extended treatment was given.

During four years and eight months since the last attempt at any treatment (human chorionic gonadotropin (Antuitrin S) and thyroid, ending 13 November 1956) the patient had grown 20.1 cm (7⅞ inches) with an average rate of 4.3 cm per year. Sexual maturity had occurred during this time, so presumably the puberty growth spurt already had occurred. In the year immediately preceding he had grown only 2.9 cm (1⅛ inches), an indication that the rate of growth was now in the decreasing phase.

When the patient was examined in July 1961 at the age of 14 years and one month, the height was 129.4 cm (50⅞ inches), the normal mean height for his age being 163.2 cm (64¼ inches), and the weight was 40.1 kg (88¼ pounds). The head was of normal configuration, but otherwise the general build and extremities were typical of achondroplasia (Figure 2). Muscles were well developed and genitalia were of adult size. X-ray bone age was read as 13½ years. Other laboratory results are listed in Table 2.

A constant intake study was performed with administration of 10 mg of HGH daily for six days. This showed an average daily nitrogen retention of 4.5 gm and an average daily calcium diuresis of 90 mg (Chart 1).



14 July 1961 — 14 years, 1 month
Height: 129.6 cm

14 June 1962 — 15 years
Height: 133.4 cm

14 June 1963 — 16 years
Height: 136.1 cm

14 July 1964 — 17 years, 1 month
Height: 137.8 cm

Figure 2.—(Case 2) Growth of patient over a three-year period of intermittent treatment with human growth hormone and thyroxine.

TABLE 2.—*Laboratory Findings in Case 2 (July 1961, unless otherwise dated)*

Protein-bound iodine—5.3 mcg per 100 ml; December 1962, 6.2 mcg per 100 ml

BEI—5.2 mcg per 100 ml

Serum Cholesterol (mg per 100 ml)—246 mg per 100 ml; December 1962, 165 mg per 100 ml (on thyroxine), July 1964, 143 mg per 100 ml (on thyroxine)

I^{131} Uptake—13 per cent in 24 hours; rose to 51 per cent after 3 doses of thyroid stimulating hormone, 5 mg every 12 hours

Serum Phosphorus—5 mg per 100 ml; August 1962, 3.9 mg per 100 ml (during control period), August 1963, 5 mg per 100 ml (end of control period)

Serum Alkaline Phosphatase—4.8 Bodansky units

Serum Electrolytes—Normal range

Blood Urea Nitrogen—16.3 mg per 100 ml

Urinary 17 Ketosteroids—3.2 mg per 24 hours; rose to 5.8 mg per 24 hours after 3 doses of ACTH gel, 10 units every 8 hours

Urinary 17 Hydroxycorticoids—6.6 mg per 24 hours, rose to 18.4 mg after ACTH stimulation as above

Urine Gonadotropins—positive at 5 and negative at 10 mouse uterine units. December 1962, positive at 20 muu (on treatment)

Glucose Tolerance Test Results (in mg per 100 ml)

	July 1961	*April 1963*	*July 1964*
Fasting	81	85	......
Postprandial			
½ hour	140	124	132
1 hour	149	110	98
1½ hours	......	......	109
2 hours	87	99	114
3 hours	89	100	108

Intelligence quotient, October 1961, 117.

Treatment was started 2 August 1961, when the patient's height was 129.6 cm (51 inches), with 5 mg of HGH daily. Buttons of tissue appeared beneath the nipples after one month, but these subsided spontaneously without interruption of therapy. Subsequent treatment, heights and bone ages are listed below, and also are shown graphically in Chart 3.

Discussion

Attempts to stimulate growth in achondroplasia have been previously reported. Whitelaw and coworkers[11] administered the anabolic agent Nilevar® (norethandrolone) to a girl seven years old. An initial spurt of growth resulted, followed by a loss of effect. HGH was used by Gershberg and coworkers[5] in a boy of 14 years; dosage was 3 mg and then 5 mg administered weekly. Small spurts of growth occurred, but there was a tendency to lose effect.

In our study, a larger dose of HGH (5 mg daily) was used. Stimulation of rate of growth in the younger patient seemed definite. It approximately doubled during the first two treatment periods as compared with the control periods. In 24 months of observation with hormone administered for less than 14 months, gain in height was 10.9 cm (4¼ inches).

Date	*Treatment*	*Height (cm)*	*Bone Age (years)*
2 August 1961 (age 14 yr. 2 mo.)	HGH 5 mg a day	129.6	13½
29 October 1961	Discontinue HGH	130.6	13½
3 February to 5 March 1961	Balance studies*	131.6	14
6 March 1962	HGH 5 mg + Na-l-thyroxine 0.2 mg a day	132.0	
16 June 1962	Discontinue all treatment	133.4	15
29 August 1962	None	134.0	15½
15 September 1962	HGH 5 mg + Na-l-thyroxine 0.2 mg a day	134.3	
26 December 1962	Same	135.0	17

---

*Constant intake studies at this point showed average daily nitrogen retention of 2.4, 2.0 and 1.0 gm on HGH doses of 10 mg, 5 mg, and 2.5 mg daily respectively. Calcium diuresis of approximately 80 mg daily occurred on the 2.5 mg dosage, but shifting baseline made estimation difficult on the other dosages. (See Chart 1). Daily nitrogen and calcium intakes during this time were 14 gm and 36 mg respectively.

Date	*Treatment*	*Height (cm)*	*Bone Age (years)*
13 April 1963	Same	135.8	17 (radial epiphyses still open)
10 June 1963	Same Discontinue 15 July 1963	136.1	17 (radial epiphyses still open)
29 August 1963	None From 8 September 1963 HGH 5 mg + Na-1-thyroxine 0.2 mg a day Discontinue 15 November 1963	136.1	
27 December 1963	None From 26 January 1964 to 5 March 1964 HGH 5 mg + Na-l-thyroxine 0.2 mg a day, then discontinue, resumed from 2 April to 12 May 1964. Then discontinue	137.9	17 (beginning fusion of radial epiphyses)
14 July 1964		137.8	18

The results in the older patient were not striking, but since the puberty spurt of growth presumably already had occurred and the rate of growth was in the decreasing phase, little was expected. In this patient the growth rate did not seem to change at first, but increased somewhat after the addition of Na-1-thyroxine to the regimen. This occurred despite the fact that thyroid function studies were all normal with the exception of a slightly low I^{131} uptake. The apparent synergistic effect of thyroid extract had been noted and reported earlier with other anabolic agents.[2] After one year of treatment (including control periods), the patient had grown 4.7 cm (1⅞ inches), a not inconsiderable amount for this phase of the growth cycle. During the 33-month period of observation, of which 21 months were months of treatment, the total growth was 8.2 cm (3¼ inches). The HGH had shown definite anabolic effects in this patient, with one of the highest degrees of nitrogen retention seen in our series. (See Chart 1.)

It should be emphasized that the amounts of growth hormone administered to these patients (5 mg daily), and also to the patients with gonadal dysgenesis,[7] were considerably larger than those which increased the rate of growth in hypopituitarism (2.5 to 5 mg three times a week). Also, the actual increase in heights was not great, but the different rates of growth during treatment and control periods would seem to indicate that HGH may have some stimulating effect in conditions other than hypopituitarism. While this conclusion is suggested by these studies, more observations will be necessary before a definitive answer can be given. Such studies may have to await the greater availability of the hormone, perhaps in a synthetic form.

Estimation of bone ages was difficult, for the deformities of the disease distorted those centers upon which estimations are traditionally based. As was noted, Dr. Steinbach elected to read changes in the less affected fingers alone, and with this method of interpretation the bone age of the patient in Case 2 was thought to increase from 13½ to 18 years in three years. The younger patient (Case 1) who had shown a bone age increase of only six months in the first 10 months of observation and treatment, then matured 12 months in the next six months. This is in contrast to our experiences using HGH in hypopituitarism[3] and in gonadal dysgenesis[7] in which conditions the bone age did not advance unduly during or after therapy.

With regard to the other laboratory studies, it can be noted in Case 2 that, as expected, the serum cholesterol dropped after the addition of Na-1-thyroxine to the regimen, although there was some fluctuation in Case 1 without the thyroxine. Serum phosphorus was somewhat higher in Case 1 dur-

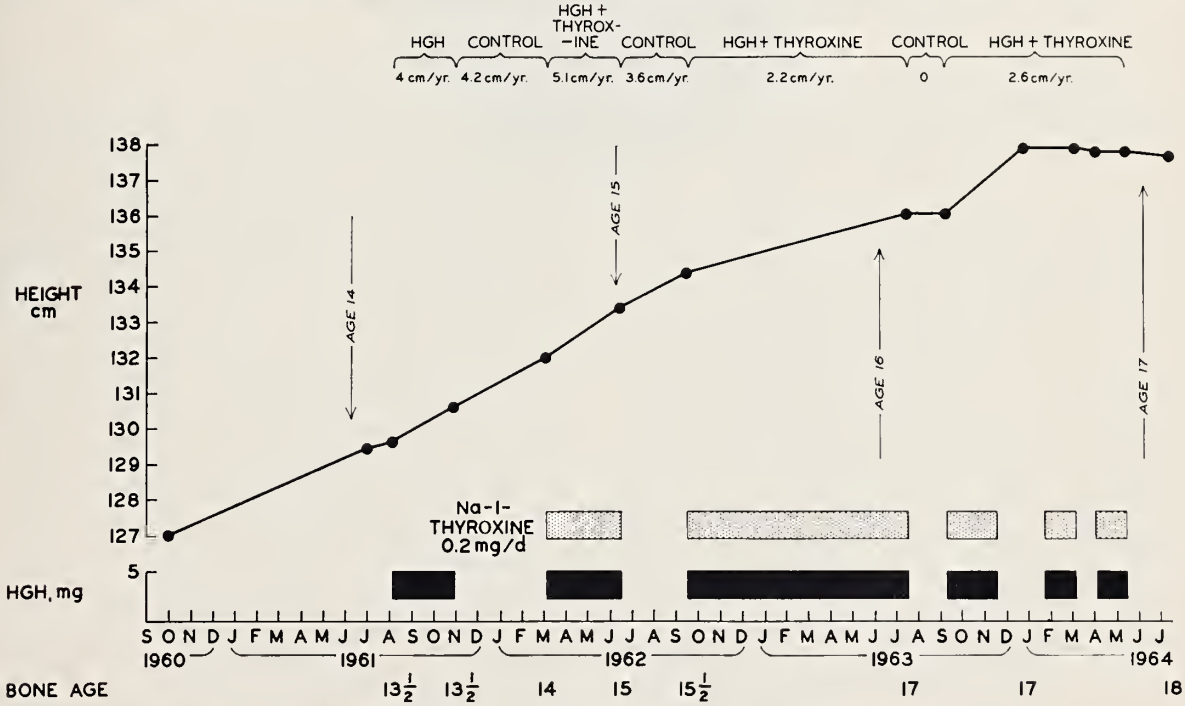


Chart 3.—(Case 2) Linear growth response to HGH and NA-l-thyroxine in achondroplasia.

ing treatment with HGH and dropped during the control period. Urine steroids were at normal levels for the respective ages. Urine gonadotropins were higher during treatment in Case 2. Repeated glucose tolerance tests in both patients did not demonstrate any diabetogenic effects. No complications of treatment were noted, with the possible exception of the transient gynecomastia noted in Case 2.

REFERENCES

1. Cole, R. D., and Li, C. H.: Studies on pituitary lactogenic hormone XIV, a simplified procedure of isolation, J. Biol. Chem., 213:197, 1955.

2. Escamilla, R. F., and Bennett, L.: Pituitary infantilism treated with purified growth hormone, thyroid and sublingual methyltestosterone, a case report, J. Clin. Endocrinol., 11:221, 1951.

3. Escamilla, R. F., Hutchings, J. J., Deamer, W. C., Li, C. H., and Forsham, P.: Long-term effects of human growth hormone (Li) in a pituitary dwarf, J. Clin. Endocrinol. and Metab., 21:721, 1961.

4. Escamilla, R. F., Hutchings, J. J., Deamer, W. C., and Li, C. H.: Clinical experiences with human growth hormone (Li) in pituitary infantilism and in gonadal dysgenesis. Program—First Internat. Cong. of Endocrinology, Copenhagen, 1960, p. 253.

5. Gershberg, H., Neumann, L., and Mari, S.: Human growth hormone in Vitamin D-resistant rickets and achondroplastic dwarfism, Fed. Proc., 21:198, 1962.

6. Hutchings, J. J., Escamilla, R. F., Deamer, W. C., and Li, C. H.: Metabolic changes produced by human growth hormone (Li) in a pituitary dwarf, J. Clin. Endocrinol. and Metab., 19:759, 1959.

7. Hutchings, J. J., Escamilla, R. F., Li, C. H., and Forsham, P. H.: Administration of human growth hormone (Li) in gonadal dysgenesis, Am. J. Dis. Child., 109:318, 1965.

8. Li, C. H. and Papkoff, H.: Preparation and properties of growth hormone from human and monkey pituitary glands, Science, 124:1293, 1956.

9. Li, C. H., Papkoff, H., and Hayashida, T.: Preparation and properties of beef (alpha core) from chymotryptic digestion of bovine growth hormone, Arch. Biochem. and Biophys., 85:97, 1959.

10. Raben, M. S.: Preparation of growth hormone from pituitaries of man and monkey, Science, 125:883, 1957.

11. Whitelaw, M. J., Thomas, S. F., Graham, W. H., and Jennison, M. H.: Die Steroidbehandlung Der Achondroplasie, Deutsche Med. Wch., 86:2159, 1961.

Marlex® Mesh in Incisional and Inguinal Herniorrhaphy

JAMES R. JOHNSON, M.D., *Los Angeles*

■ *Marlex® mesh was used in 31 cases of inguinal herniorrhaphy and in 15 cases incisional herniorrhaphy in a five-year period. In 14 of the inguinal and six of the incisional cases the hernias were recurrent. Marlex® mesh was used in one case to reenforce the transthoracic repair of eventration of the diaphragm, and in another to reenforce the transthoracic repair of an esophageal hiatal hernia.*

There were no recurrences. In one case after inguinal herniorrhaphy the mesh was removed because of persistent drainage. Wound infections occurred in two patients with incisional herniorrhaphy, and two others had the accumulation of serous fluid subcutaneously necessitating aspiration of fluid.

EXPERIMENTAL AND CLINICAL studies[1-9] with Marlex® mesh in the past five years have indicated that as a reenforcing agent or to fill a tissue defect in incisional, diaphragmatic and groin herniorrhaphy, it is superior to Teflon,® Mersilene,® Dacron® and Nylon® mesh. It produces fewer adhesions when placed in the peritoneum or when used for repair of a diaphragmatic defect. It withstands infection better with less chance of rejection of the mesh. In two months it is well bonded to the surrounding tissue. Now that Marlex® mesh may be sterilized by autoclaving, instead of boiling, one of the problems—infection—has been lessened.

In 1960 and 1961, I used Teflon® mesh as a reenforcing mesh in repair of eight inguinal and four incisional hernias and in none of these cases was there either infection or rejection of the mesh. In one patient who had herniorrhaphy for recurrent inguinal hernia a small recurrence of herniation developed following repeated asthmatic attacks.

In a five-year period beginning in 1960 when I began using Marlex® mesh instead of Teflon® mesh, I used the material in 31 inguinal and 15 incisional repairs. In two cases it was placed on the thoracic side of the diaphragm.

Because of the possibility of infection and seroma, Marlex® mesh should not be used routinely. The material was used to reenforce inguinal herniorrhaphy in patients with recurrent inguinal hernias or large direct or sliding inguinal hernia particularly if the fascial structures were weak or the patient's occupation required heavy lifting. In incisional herniorrhaphy Marlex® mesh was used to reenforce recurrent hernias or those so large that the fascial edges of the hernial ring could not be approximated.

Submitted 17 February 1966.

Reprint requests to: 3701 Stocker Street, Los Angeles, California 90008.

Inguinal Herniorrhaphy

In 14 of the 31 inguinal cases the patient had had one to three recurrences before the use of Marlex® mesh. In the other 17 cases the lesions were large direct or sliding inguinal hernias in patients who had weak fascia or who did very heavy lifting for a livelihood. The mesh was always placed beneath the external oblique fascia and sutured to fascial structures with nonabsorbable suture material, either cotton or Supramid.® In one instance, it bridged a defect in a patient who twice had had inguinal herniorrhaphy, with recurrence. In the other 30 cases it was used to supplement the tissue incorporated in the repair.

There have been no recurrences or instances of subcutaneous serous fluid accumulation. The only complication was wound infection with persistent sinus drainage in one patient. In this case the mesh was removed two months after operation.

Incisional Herniorrhaphy

Six of the 15 incisional hernias were recurrent. One patient had had four operations for repair, with tantalum mesh inserted and removed in one instance. All incisional hernias were considered very large, involving defects covering one-fourth or more of the abdominal wall. Two patients had multiple hernias.

Whenever possible the Marlex® mesh was placed beneath the fascia and the fascial defect was closed over it; but if the tissues were so fused that this could not be done, the fascia was repaired, if possible, and the mesh sutured over it. In five cases the mesh was used to bridge large fascial defects which could not be repaired. In those cases the hernial sac was inverted as much as possible and the mesh was sutured to firm fascia as an onlay graft, using two rows of closely placed, interrupted, nonabsorbable (cotton or Supramid®) sutures. The point of entry for all sutures was at least two centimeters from the edge of the hernial ring.

All wounds were drained by catheters connected to suction for several days, until drainage became slight.

There have been no recurrences. Wound infection occurred in two cases. In one of them incision and drainage were carried out and the wound healed in three months. In the other the patient, an 80-year-old woman, died of renal failure two months after operation without complete healing of the wound. This wound had been contaminated at the time of operation for recurrent small intestinal adhesive obstruction.

In two cases, subcutaneous serous fluid accumulation required aspiration with a needle, once only in one case, but repeatedly over a period of four months in the other.

Diaphragmatic Defects

Marlex® mesh was used in one case to reenforce a transthoracic repair of eventration of the left diaphragm. There were no postoperative complications and the result was excellent when the patient was last observed at the end of three years.

In another patient the material was used for reenforcement in the transthoracic repair of a large esophageal hiatal hernia. No complications developed.

REFERENCES

1. Adler, R. H., Mendez, M., and Darby, C.: Implanted mesh for wound strength, Surgery, 52:898-904, December 1962.
2. Adler, R. H.: An evaluation of surgical mesh in the repair of hernias and tissue defects, Arch. Surg., 85:836-844, November 1962.
3. Blaisdell, W., and Hall, A. D.: Use of knitted Marlex® mesh in the repair of ventral hernias, Am. J. Surg., 110:897-902, December 1962.
4. Gorman, W. C., Flynn, G. F., Lapley, Jr., D., and Weisel, W.: Synthetic materials for bridging diaphragm and chest wall defects, Arch. Surg., 82:863-869, June 1961.
5. Hafner, C. D., Wylie, Jr., J. H., and Brush, B. E.: Petit's Lumbar hernia: Repair with Marlex® mesh, Arch. Surg., 86:180-189, February 1963.
6. Usher, F. C., and Wallace, S. A.: Tissue reaction to plastics—a comparison of nylon, dacron, teflon, and Marlex,® Arch. Surg., 76:997-999, June 1958.
7. Usher, F. C.: A new technique for repairing large abdominal wall defects, Arch. Surg., 6:870-877, June 1961.
8. Usher, F. C.: Braided Marlex® suture, Arch. Surg., 83:203-204, August 1961.
9. Usher, F. C.: Hernia repair with Marlex® mesh, Arch. Surg., 84:325-328, March 1962.

IMPETIGO

Bacteriologic Features and Renal Involvement

STANTON E. SHULER, M.D., *New Orleans*

■ *One hundred children with impetigo were studied with particular emphasis upon the organism causing the infection and associated renal complications. In 50 per cent of cases, Group A beta-hemolytic streptococcus grew on cultures of material from the lesions, and evidence of recent infection with this organism as shown by an elevation of antistreptolysin O titer was present in an additional 17 per cent of cases.*

Acute glomerulonephritis developed in three of the 66 children with bacteriologic or serologic evidence of streptococcal infection. Four other children in this group and nine children with staphylococcal impetigo had unexplained microscopic hematuria.

All children with nephritis already had evidence of the disease when first seen. In most of those with unexplained hematuria, this condition was detected at the first visit. Hematuria developed in others while they were receiving systemic antibiotics. The significance of isolated microscopic hematuria is uncertain, but is seen often in association with cutaneous infection with both staphylococcus and streptococcus. Microscopic hematuria as defined is apparently not prevented by antibiotic therapy.

If acute glomerulonephritis that follows streptococcal cutaneous infection is to be prevented, streptococcal impetigo will have to be treated promptly after onset.

IMPETIGO is one of the most common cutaneous diseases of childhood. On culture, coagulase-positive Staphylococcus aureus or Group A beta-hemolytic streptococcus, or both, are identified in almost all instances. The incidence of recovery of these organisms seems to vary with the geographic area and the nature of the population studied.* Acute glomerulonephritis, the most feared complication of streptococcal cutaneous infection, occurs in from zero to 68 per cent of cases.[1,3,4,5,8,9] Lesions heal as rapidly with topical as with systemic therapy, although systemic treatment is more reliable.[5,8] What, then, should be the indication for systemic therapy, and does therapy prevent renal complications? In an attempt to answer these questions a study designed to determine the incidence of streptococcal impetigo in San Diego, California, as well as the incidence of renal complications was undertaken.

Material and Method

One hundred children with impetigo, ranging in age from one to 11 years, seen at the U.S. Naval Hospital, San Diego, between July 1964 and July 1965 were studied. Ninety-six of the children were Caucasian and four were Negro.

At the first visit of a child with a cutaneous in-

From the Department of Pediatrics, United States Naval Hospital, San Diego, California. At the time this article was written, the author was on active duty as a Lieutenant Commander, Medical Corps, United States Navy Reserve.

Submitted 11 January 1966.

Reprint requests to: Department of Pediatrics, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121.

*Reference Nos. 2, 4, 5, 8, 10.

fection, a note was made of the duration and distribution of the lesion, as well as other pertinent abnormalities. Material taken from the lesion and from the throat was planted on sheep blood agar culture media. If a crust had formed on the lesion, the culture was taken from beneath a crust that had been lifted. Antistreptolysin O titer was drawn, and routine urinalysis and a test of the urine for occult blood were carried out. Initial therapy consisted of washing with a hexachlorophene-containing soap and topical application of bacitracin ointment (U.S.P., 500 units per gram). If the disease was considered to be extensive, systemic administration of antibiotics was prescribed at the first visit. At weekly intervals for two weeks after the first visit, the child's progress was noted and the urine was examined. Two weeks from the first visit an antistreptolysin O titer was again drawn. If Group A beta-hemolytic streptococci were recovered from culture of material from the throat or the lesion, phenoxymethyl penicillin was prescribed in doses of 125 mg to 250 mg by mouth four times daily for 10 days. Children allergic to penicillin were given erythromycin.

Results

Table 1 shows the distribution of cases according to type of infection causing impetigo. The distribution according to age and sex was the same in all groups.

Antistreptolysin O titer was considered to be significant if it was 250 Todd units or more, or if between the first and second determination there was a two-tube titer rise. The nine children with elevated antistreptolysin O titers and staphylococcus cultured from the cutaneous infection had negative throat cultures for Group A beta-hemolytic streptococci.

Sixteen children had renal involvement. Nine children with staphylococcal cutaneous infection had microscopic hematuria.* This was noted on initial urinalysis in five children, on the second in three, and on the third in one child. None of these children had bacteriologic or serologic evidence of streptococcal infection. All seven children with concurrent hematuria or acute nephritis† and streptococcal cutaneous infection had elevated antistreptolysin O titers. The urine was abnormal on initial examination in all but two children who had hematuria with the combination of staphylococcal and streptococcal cutaneous infection. Microscopic hematuria cleared in all instances by the third week after the patient was entered in the study and did not recur.

The average time required for healing of the various types of impetigo was about the same regardless of the type of therapy. Also, there was no correlation between response to therapy and how long the lesions had been present at the time of the first examination.

Cellulitis developed in two children with cutaneous infection. Three had symptomatic acute otitis media, and four had symptomatic pharyngitis (all proved by culture to be streptococcal). One child had a urinary tract infection which later proved to be associated with bladder neck obstruction and right ureterovesical reflux.

TABLE 1.—*Summary of Clinical and Laboratory Findings in Patients with Impetigo as Related to Infecting Organism*

	Staphylococcus	*Staphylococcus and Streptococcus*	*Streptococcus*	*E. Coli*
Number of patients	49	24	26	1
Duration of illness at first visit—				
Range	3 days to 3 months	2 days to 4 weeks	2 days to 5 months	11 days
< 7 days	50 per cent	72 per cent	65 per cent	
< 14 days	88 per cent	94 per cent	75 per cent	
Number of patients with positive throat cultures—				
Staphylococcus	20	4	8	0
Streptococcus	7	14	13	0
Number of patients with elevated antistreptolysin O titer	9	16	14	0
Number of patients with renal involvement—				
Hematuria	9	2	2	0
Nephritis	0	1	2	0
Healing time (average number of days)	Local infection 10.4 Systemic infection 11.5	12.5	11.0	6

---

*Microscopic hematuria was defined as the presence of at least ten erythrocytes per high power field in a centrifuged specimen on two or more urinalyses.

†Acute glomerulonephritis as seen in this study was typical clinically, on examination, and from the laboratory determinations.

Discussion

Impetigo seems to be predominantly of staphylococcal origin.[2,8,10] Parker and Williams[10] reported that staphylococcal impetigo was twice as common as streptococcal impetigo, but the incidence varied from year to year. According to Barrow,[2] it is four times as common. Barrow showed that the phage type of staphylococcus causing impetigo is frequently phage type 71. Markowitz and coworkers[8] found that only 22 per cent of their patients had streptococcal impetigo and 40 per cent had staphylococcal impetigo. In 38 per cent of cases, culture of material taken from the noses of patients with staphylococcal impetigo grew phage type 71, which substantiated Barrow's observation that phage type 71 is often associated with staphylococcal impetigo. In only 8 per cent of the cases of streptococcal impetigo were they able to isolate the organism from the throat. In 50 per cent of the patients in the present study, Group A beta-hemolytic streptococcus was isolated from the lesions alone. This incidence, however, might vary from year to year. In at least half of the patients with streptococcal impetigo this organism has been isolated from the throat. In 83 per cent of children with impetigo Burnett[4] found bacteriologic or serologic evidence of streptococcal infection, whereas Markowitz and associates[8] reported an incidence of 48 per cent. In the present study bacteriologic or serologic evidence of streptococcal infection was obtained in 67 per cent of cases.

The nature of the lesion in the individual case is of little help in predicting the type of organism. It has been possible to grow Group A beta-hemolytic streptococcus from bullous lesions and coagulase-positive Staphylococcus aureus from frank cellulitis. In general, however, lesions of the face and upper lip were more often found to contain streptococci than were lesions elsewhere.

Streptococcal infection of the skin is a common forerunner of acute glomerulonephritis. McCullough and associates[9] obtained a history of cutaneous infection in 33.8 per cent of patients with acute nephritis. Blumberg and Feldman[3] noted that 68 per cent of patients they observed with nephritis had previous cutaneous infections. In two prospective studies in children with bacteriologic or serologic evidence of streptococcal infection of the skin, a similar incidence of post-streptococcal glomerulonephritis was obtained. Acute nephritis developed in two of 42 patients (4.76 per cent) studied by Burnett[4] and in 3.4 per cent of 144 patients studied by Markowitz and coworkers.[8] In the present study three of 66 patients (4.5 per cent) with bacteriologic or serologic evidence of streptococcal infection had acute post-streptococcal glomerulonephritis.

In the present study all children with acute glomerulonephritis had the disease at the first visit. Five children in the series of Markowitz and coworkers[8] in whom acute glomerulonephritis developed had evidence of the disease at the first visit. It would therefore be difficult to reduce this incidence unless patients could be treated at an earlier date. Stetson and coworkers[12] showed that early treatment of streptococcal pharyngitis reduced the incidence of acute glomerulonephritis.

Can the unexplained hematuria be prevented by previous antibiotic therapy? Markowitz and coworkers[8] reported that in five of 14 patients with hematuria this symptom developed after administration of penicillin for at least one week. Another eight patients had hematuria when first examined. Thus, in 13 of 22 patients the hematuria was present at the initial visit or developed during administration of antibiotics. Of these 22 children, 15 had bacteriologic or serologic evidence of streptococcal infection. In the present study 10 of the 16 patients had hematuria at the first visit, and hematuria developed in two on the seventh and tenth days, while they were receiving penicillin. The other four children had staphylococcal impetigo and no serologic evidence of streptococcal infection. It is difficult to determine the significance of hematuria associated with staphylococcal impetigo. Stetson and coworkers[12] reported that during the first few days of proved streptococcal pharyngitis, nonspecific hematuria occurred and it seemed to be more frequent after type 12 streptococcal infection, although it occurred with other types as well. Acute glomerulonephritis did not necessarily develop in these patients, and this conceivably could happen in other infectious processes as well.

Markowitz and associates[8] noted no definite abnormality in the two children with unexplained hematuria on whom percutaneous renal biopsy was performed. Unfortunately, in the present series biopsy was not done on any children with only unexplained hematuria. Two of the three children with clinical manifestations of glomerulonephritis on whom renal biopsy was done had typical light, electron and fluorescent microscopic evidence of poststreptococcal glomerulonephritis.[6] The prognosis for this lesion is excellent.[11]

Whether poststreptococcal complications associated with impetigo can be prevented cannot be determined from the data in this study. One reason for this might be the delay between onset of cutaneous infection and the first visit to a physician. If nephritis is to be prevented treatment must be begun early.[12] Therapy seems to have little effect on development of hematuria.

REFERENCES

1. Addis, T.: Glomerular Nephritis. Diagnosis and Treatment, The Macmillan Co., New York, 1948.
2. Barrow, G. I.: Clinical and bacteriologic aspects of impetigo contagiosa, J. Hyg., 53:495, December 1955.
3. Blumberg, R. W., and Feldman, D. B.: Observations on acute glomerulonephritis associated with impetigo, J. Pediat., 60:677, May 1962.
4. Burnett, J. W.: Management of pyogenic cutaneous infections, New Engl. J. Med., 266:164, 25 January 1962.
5. Burnett, J. W.: The route of antibiotic administration in superficial impetigo, New Engl. J. Med., 268:72, 10 January 1963.
6. Feldman, J. D., Mardiney, M. R., and Shuler, S. E.: Poststreptococcal glomerulonephritis. Immunology and morphology of acute poststreptococcal glomerulonephritis, Lab. Invest., 15:283, January 1966.
7. Kleinman, H.: Epidemic acute glomerulonephritis at Red Lake, Minnesota Med., 37:479, July 1954.
8. Markowitz, M., Bruton, H. D., Kuttner, A. G., and Cluff, L. E.: The bacteriologic findings, streptococcal immune response, and renal complications in children with impetigo, Pediatrics, 35:393, March 1965.
9. McCullough, G. C., Coffee, J. Y., Trice, P. A., Jr., Stone, J. J., and Crandall, .H. L.: Acute glomerulonephritis: impetigo as an etiologic factor, J. Pediat., 38, 346, March 1951.
10. Parker, M. T., and Williams, R. E.: Further observations on the bacteriology of impetigo and pemphigus neonatorum, Acta Paediat., 50:101, March 1961.
11. Perlman, L. V., Herdman, R. C., Kleinman, H., and Vernier, R. L.: Poststreptococcal glomerulonephritis. A ten-year follow-up of an epidemic, J.A.M.A., 194:63, 4 October 1965.
12. Stetson, C. A., Rammelkamp, C. H., Jr., Krause, R. M., Kohen, R. J., and Perry, W. D.: Epidemic acute nephritis: studies on etiology, natural history and prevention, Medicine, 34:431, December 1955.

Methods of Therapy in Alcoholism

MAX HAYMAN, M.D., *Los Angeles*

■ *Although the philosophy of the community mental health center has been applied to alcoholism since the early part of this decade, it has been pursued much more intensively in recent years, and there has been a decentralization in the management of alcoholics in a series of stages from the jail or workhouse to the state hospital and to the clinic and the community. The medical practitioner now has opportunity to treat the alcoholic in private practice.*

Advances have been made in two directions. Advances in medical management have included reinforcement of the importance of hydration and electrolyte balance, particularly magnesium. Psychopharmacology has contributed three drugs particularly important in the management of acute alcoholism and its complications. These drugs are chlordiazepoxide, chlorpromazine, and thioridazine. Another drug, Antabuse, when properly used, has proven extremely valuable as a deterrent.

Equally important have been administrative advances. The importance of the environment and its manipulation has been recognized, and a series of institutional and non-institutional resources, such as clinics, half-way houses, foster homes, and Alcoholics Anonymous has made it less likely that a patient will be turned away without help.

INTEREST IN ALCOHOLISM and alcoholics has increased considerably in the past decade. The lay organizations which once functioned desultorily have become stronger and more influential. One example of this is the National Council on Alcoholism, which now has an active medical director. Another is the North American Association of Alcoholism Programs whose goals for the betterment of the condition of the alcoholic have been progressively broadened and now include almost every facet of the problem of alcoholism. Numerous public and private agencies have accepted the task of informing the public, of changing invidious attitudes to alcoholics and of providing the best facilities for the amelioration of the problem. As knowledge has increased, the complexity of the problem has become more apparent, and there has been an involvement of progressively more types of personnel and more of the caring professions in its management.

Concurrently there is an increasingly objective and perhaps sympathetic attitude toward alcoholics, which in itself is partly a reflection of a generally more liberal community attitude toward psychiatric disorders. Alcoholics Anonymous has been a powerful influence in upgrading the status of the alcoholic and of those who treat him, not only through its capacity to ensure sobriety for

---

Alcoholism Research Clinic, Department of Psychiatry, U.C.L.A. Center for the Health Sciences, Los Angeles, and Compton Foundation Hospital (Vista Hill Psychiatric Foundation).

This investigation was supported by research grant #110 from the California State Department of Public Health, and by the Compton Foundation Hospital (Vista Hill Psychiatric Foundation).

Presented before a Joint Meeting of the Sections on Psychiatry and Neurology and General Practice at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Department of Psychiatry, U.C.L.A. School of Medicine, Los Angeles, California 90024.

many alcoholics, but also through its 12 steps and 12 traditions, which have kept it on a path free of divisive influences and with a single-minded devotion to its goals.[2] The concept of alcoholism as a disease has been well publicized, and even though it required a pronouncement from both the American Medical Association and the American Hospital Association to have it be so considered, such a promulgation has lent considerable respectability to the condition.[9] The change in the attitude toward alcoholism is epitomized by the change in the management of the alcoholic offender by our most conservative social force—the law. Municipal court judges, instead of summarily fining alcoholics or sentencing them to prison terms, now frequently look upon them as individuals instead of as part of a nameless, rather unpleasant mass of malodorous humanity. These judges are now asking what they can do to help such unfortunate persons.

The philosophy of the Community Mental Health Center, so much in the news recently, has been applied to alcoholism since the early part of this decade and in actuality predated the current concepts as applied to mental health.[3] The author and many others have utilized all five services included in this program—namely, inpatient care, outpatient care, emergency service, consultation and education and partial hospitalization. Since 1957 we have used day hospitals, sometimes for semi-acute and occasionally for more acute alcoholic states.[5] At first, as alcoholism became recognized as a medical problem rather than errant or criminal behavior, many patients were sent to state hospitals instead of to jails, but there they had essentially no therapy. The hospitals therefore differed from jails only in their more pleasant surroundings. More recently, however, there has been a progressive decentralization in the management of alcoholics, which has included a series of stages from jail or workhouse, to state hospital, to clinic, to community.

A logical development, consistent with the return of the problem to the community, has been the assignment of the organization of alcoholism services to the local public health departments. The State Department of Public Health in California has been especially active in its management of the problem of alcoholism; and, beginning this year, the origination of alcoholism programs has been entrusted to the local public health officer, who brings together the various services necessary for a coherent, integrated program. But the public health perspective on alcoholism does not preclude the medical practitioner from taking part in the provision of services; indeed, it will bring many a practitioner into an active relationship with the treatment services for alcoholics.

The evolution of these services will be further advanced when the concept of alcoholism as a medico-psycho-social disorder filters through to a greater number of medical practitioners. As more patients are benefited by the techniques now available, more pressure is brought to bear on the private physician to provide additional services for the alcoholic. Neither the patient nor the medical practitioner will long be satisfied with no more than the prescription of a sedative. Furthermore, as our techniques become more highly developed, as we have a broader, more objective view of the disorder, and as the punitive approach is eliminated, the distaste the medical practitioner has had will progressively decrease.

An example of the change that the objective approach can make to alcoholism is the changing attitude toward motivation in the alcoholic. Previously a circular impasse would develop, expressed by the dictum that the alcoholic must be well motivated to improve, but could not improve until he was well motivated. It is gradually being accepted that the defective motivation is as much a part of the picture of alcoholism as is the drinking itself, and we are now accepting the responsibility of inducing motivation and studying the means of doing so.[6] One of the two principal methods of inducing motivation, that of coercion, for example, can now be applied in a flexible and non-punitive manner; and the other, the giving of "tender loving care," can be done with the therapeutic rather than the do-gooder attitude.

Advances in Medical Management

Chart 1 shows the procedures most commonly associated with the medical management of alcoholics. In the acute phase of alcoholism there has been a reinforcement of the importance of appropriate hydration and of electrolyte balance, including magnesium. Mortality from delirium tremens has progressively decreased from over 30 per cent to as low as 4 per cent or even in one report to zero.[4] With the development of psychopharmacology, three drugs particularly have stood out as helpful in the management of acute alcoholism and its complications. These drugs are chlordiazepoxide (Librium®), chlorpromazine (Thorazine®) and thioridazine (Mellaril®).

Along with this, there has been an increased sensitivity to the need for alcoholics in acute states to have the best medical care possible. More and more hospitals and physicians have accepted the responsibility of treating alcoholics in the acute state. Many papers have been written showing that an alcoholic is rarely disruptive on the wards of the general hospital, and the attitude of the medical practitioner, the administrator and the nurse is becoming more objective and tolerant.[1]

In the chronic phase also there have been a number of advances. Drugs have not as yet proved very helpful in this phase, but the search is continuing quite actively. There have been some favorable references to the use of chlordiazepoxide (Librium®), but some recent papers, and some of our work at the UCLA Alcoholism Research Clinic, suggest that it might possibly be deleterious in chronic alcoholism.[13] In spite of many favorable reports on the use of lysergic acid diethylamide (LSD) in alcoholism, adequate studies demonstrating its usefulness have not yet been published and therefore this drug must still be considered experimental. Recently some communications have suggested it is of no value.[8,14] In any case, in the chronic phase drugs must be used sparingly and carefully. The principal drug advance has been in the use of disulfiram (Antabuse®). This is an extremely important tool for the medical practitioner and with the ordinary alcoholic patient has been one of the main reliances. In many areas Antabuse® has come into disfavor because it is not used properly. It must be administered as part of a consistent, planned program for the alcoholic in which he receives regular follow-up, counseling or psychotherapy. Handing out a month's supply of Antabuse® without further relationship with the patient is useless.

Another advance of great help to the medical practitioner is the accessibility to him of both brief and intensive courses in psychiatry. Over 4,000 physicians, 57 per cent of whom are general practitioners, have taken them thus far, making them the most popular courses offered. They not only give the necessary psychiatric or objective orientation to the physician, but also an understanding of "what makes the patient tick" and provide the background for psychotherapy and counseling. My

TYPE OF MANAGEMENT	TYPE OF PERSONNEL											
	PHYSICIAN INCL. PSYCHIATRIST	PSYCHOLOGIST	SOCIAL WORKER	REHABILITATION WORKER	ALCOHOLICS ANONYMOUS	RELIGIOUS COUNSELOR	NURSE	JUDGE	ALCOHOLISM COUNSELOR	PROBATION OFFICER	TEACHER	COORDINATOR
MEDICAL MANAGEMENT												
PHARMACOLOGICAL	•											
BIOCHEMICAL	•											
PHYSIOLOGICAL	•											
PSYCHOLOGICAL :												
INDIVIDUAL	•	•										
GROUP	•	•	•									•
FAMILY	•	•	•									•
SOCIAL MANAGEMENT												
INFORMATION & EDUCATION	•	•	•	•	•	•	•	•	•	•	•	•
RECOVERY HOME	•	•	•	•			•					•
FOSTER HOME	•	•	•	•			•					•
COORDINATOR	•	•	•	•			•					
ALCOHOLICS ANONYMOUS					•							
RELIGIOUS GROUPS						•						
LAW COURTS								•		•		•
INDUSTRIAL	•								•			
LEGISLATION	•							•				
RESEARCH	•	•										
CLINICS	•	•	•	•			•					•
STATE HOSPITALS	•	•	•		•		•					•

Chart 1.—Management of Alcoholism and Types of Personnel Utilized.

own experience indicates that a continuing preceptorship, in which a psychiatrist or medical practitioner who is experienced in the management of alcoholic patients regularly provides consultation and supervision to the medical practitioner, is the most satisfactory learning situation.

Advances in Social Management

I use the term *social* to indicate that the problem of alcoholism consists of considerably more than prescribing medication and fluids or even psychotherapy. The environment and its manipulation may at times be more necessary than medical or psychiatric sessions with the patient. The exigencies of the treatment of alcoholism have brought about a change in the attitude of the medical practitioner to such administrative needs. A recovery home, for example, may mean the difference between success and failure for the alcoholic, and it is impossible to treat him solely as an individual without attention to his family, his occupation or his embroilment with the law. The treatment of the whole man is necessarily changing from a vague concept to a practical reality.

A number of facilities have been created for the management of alcoholics. Just as the stroke of a legislative pen can create thousands of “alcoholics,” another stroke can provide therapeutic facilities for them. The California Legislature is making provision for a large number of clinics, recovery homes and other resources which often ensure the availability of help to the alcoholic patient. The medical practitioner can be the key man in such facilities if he has the motivation to treat alcoholics, will fit himself with a modicum of training, and will develop an objective attitude to the alcoholic. The ubiquitous skills of the practitioner often make him such a central figure and force him into a position of leadership of the team. If he defaults the responsibility, other disciplines move into the vacuum, and some facilities for alcoholics are directed by psychologists or social workers, not all of whom are qualified to head them.

It can be seen in Chart 1 that the skills of the medical practitioner are applicable to almost every kind of management the alcoholic may require. The resources named are self-explanatory with the exception of the coordinator. Most commonly, for example, in a clinic setting the social worker, most often a woman, takes care of the manifold problems of the alcoholic, and acts as coordinator. She is a liaison between the physician and the family or the employer or the law enforcement agencies. The presence of a coordinator can make it more feasible for the medical practitioner to undertake the management of alcoholic patients in a private practice setting. A group of physicians can engage a social worker or nurse, or possibly the state should provide a skilled person. A mature college woman, educated in the appropriate techniques, as Margaret Rioch has demonstrated, can function quite adequately in such a position.[12] Thus the role of the coordinator becomes an extension of that of the practitioner, relieving him of many tasks while he retains his management of the situation. If the coordinator is capable, she—and most often the coordinator is a woman—can do a type of therapy or counseling. Indeed, in my own work I have often found it advantageous to split the transference relationship between the physician, as the masculine principle, and the coordinator, as the maternal, nurturing person.

Aids for the Medical Practitioner

There are a number of methods and aids for the medical practitioner to use in his battle against alcoholism. They have been discussed at greater length in other publications[7] and will be dealt with briefly here.

Social Reintegration of the Alcoholic

The alcoholic, even though he may appear poised and outgoing, may be extremely shy and sensitive, and convinced he is unlikable. In time he may therefore withdraw and his personality and his social and personal skills deteriorate. Accordingly, he may need retraining and reexposure to social situations to regain his confidence. This may be provided through referral to a day hospital, or to a recovery house. There are many social organizations for recovered patients which give a group atmosphere, and earlier interests and activities of the patient may be reactivated through contact with such groups.

Vocational Rehabilitation of the Alcoholic

There are many state, federal and local programs for rehabilitation, assuming the patient has a sufficient impairment to qualify, as well as the potential to return to gainful employment. There may be vocational testing, counseling, training as well as job placement and follow-up. Federal funds are often harder to acquire for alcoholics, however. An employment counselor is often an effective intermediary between the patient and employer, also, and can offer some support to the alcoholic. The medical practitioner can help by giving appropriate background information and prognosis.

Insurance for the Alcoholic

Most health insurance policies in the United States do not provide for treatment of the alcoholic. Yet it is very important that, when the alcoholic does "surrender," immediate facilities be available to him. One of the major problems is the feeling that much of the patient's problem lies within his control, and the concomitant feeling that facilities may therefore be overused and privileges abused. Yet, a few state insurance programs—that of California, for example—do recognize alcoholism as an illness and provide for it in the state disability program.

Clergymen and the Alcoholic

Clergymen sometimes feel that the approach to the alcoholic should be entirely spiritual and are reluctant to turn to secular agencies, including Alcoholics Anonymous. Some, however, have adopted a more modern viewpoint and have begun to treat alcoholism as a disease. Although 77 per cent of clergymen failed to respond to the New York Alcoholism Study, it is hoped that they will continue to become more alert to their opportunities to institute helping techniques at an early phase of the alcoholic's illness.[11]

Industrial Programs

As industry becomes more aware of the value of providing alcoholics with counseling and treatment, more and more companies are giving such help. These companies have found that when an alcoholism counselor is appointed, alcoholics "come out of the woodwork" and soon flood him with requests for help. He can then refer them to any of many sources of outside help, often Alcoholics Anonymous. If the medical practitioner makes the diagnosis before it comes to the attention of the company, he can encourage the worker to go on the company program. This may have several advantages besides increased motivation—the open acknowledgment of the problem, daily supervision at work, and the possibility of sick benefits.

Public Health Department

In many states, the departments of public health have a Division of Alcoholism. Most of them have publications available on the problems of alcoholism and also offer special prevention and control programs, as well as providing community services, professional training, public information, evaluation, pilot projects and research. They have resources for case finding, counseling, diagnostic and referral centers, emergency care, hospital and clinic treatment, and rehabilitation services. They often also take on the problem of coordinating research, education and service.

Law and the Penal System

Frequently alcoholics, including those from the higher socioeconomic brackets, become involved in legal difficulties, such as drunk driving or disturbing the peace. Sometimes the practitioner is called upon for advice in such cases, and can use or advise court facilities or programs, if they are available. Some courts have rehabilitation programs connected with them, or quite adequate facilities for treatment. In those cases where coercion may be helpful, it may even be best to advise that the alcoholic serve a sentence or go on probation.

State Hospitals

State hospitals have often been used as a referral facility by both the medical practitioner and the courts, although frequently the alcoholic resisted it. In recent years involuntary commitment has become less and less frequent, apparently on the mistaken theory that if coercion is used the treatment may not be effective. Sometimes only physical treatment is available in the state hospitals, although a recent survey indicated that more of them now have adequate treatment programs.[10] In any event, a stay in hospital takes the alcoholic out of circulation for awhile, permitting bodily recuperation and interruption of the vicious drinking cycle.

Medical Organizations

An increasing number of local and state medical organizations are appointing committees on alcoholism, some of which act in conjunction with other organizations. Together they have considerable influence on various state or local governmental groups. Local psychiatric societies also frequently have committees on alcoholism, some of which are extremely active, providing lists of psychiatrists willing to accept such patients, or lecturing to lay or professional groups. Advice and guidance are often available.

Psychiatrists

Although many psychiatrists will not treat an alcoholic patient, it is wise to select one who will be available for such treatment or consultation as may be necessary. Psychiatric organizations have sponsored many courses in psychiatry, which have proved extremely popular; have generally been encouraging the medical practitioner to handle as large a number of patients with emotional problems as is feasible and have tried to provide the training and facilities. Psychiatrists may thus serve as referral "facilities," as consultants, as educators and as co-workers and co-reseachers in the field along with medical practitioners.

Roster of Referral Facilities

The medical practitioner should be aware of referral facilities and sources of aid and keep a personal file of them. This is particularly applicable in the case of the alcoholic who is unable to tolerate waiting. When he agrees to accept help, he expects to receive it "right now." The medical practitioner should decide as soon as possible whether he will treat the alcoholic in the acute phase only, whether he will provide treatment for the chronic phase, or will refer him to other resources. The medical practitioner should have the names and addresses of these sources, many of which he can get from rosters published by various groups, listing such facilities as clinics, social agencies and hospital outpatient departments. He should also have a list of other physicians and psychiatrists willing to help.

The treatment resources for the medical practitioner are shown in Chart 2. These are correlated with the psychiatric diagnosis and socioeconomic status. The broad spectrum of therapy which the medical practitioner can provide is illustrated, as well as the appropriate treatment for a particular type of patient. It will be noted that intensive insight therapy at one extreme range of alcoholism is applicable only to a small percentage of patients, who have a psychoneurotic

CHRONIC ALCOHOLICS
TREATMENT AND CLASSIFICATION

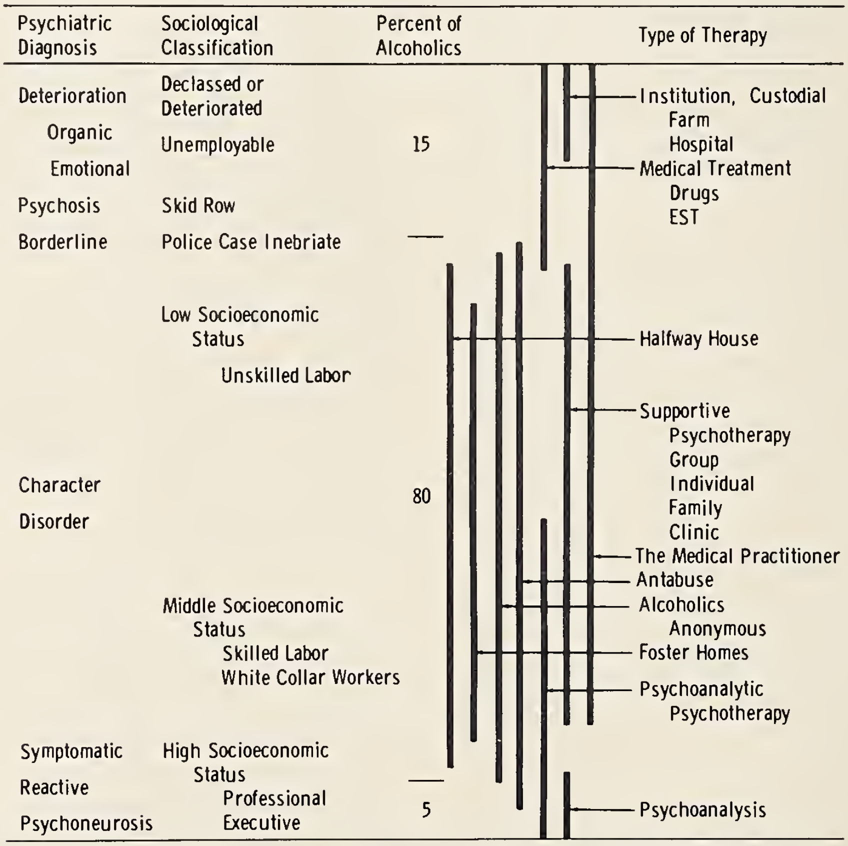


Chart 2.—Chronic Alcoholics, Treatment and Classification, Reproduced with Permission from Hayman, M. Alcoholism: Mechanism and Management, Charles C Thomas, Springfield, Illinois. To be published. EST=Electroshock therapy.

reactive or symptomatic type of alcoholism. At the other extreme only institutional, drug or physical types of treatment are possible, since the patients are the deteriorated or psychotic types of alcoholics. In between these extremes the several types of treatment can be used, sometimes more than one at a time.

GENERIC AND TRADE NAMES OF DRUGS

Chlordiazepoxide—*Librium.*
Chlorpromazine—*Thorazine.*
Thioridazine—*Mellaril.*
Disulfiram—*Antabuse.*

REFERENCES

1. A study on the nonsegregated hospitalization of alcoholic patients in a general hospital, Hospital Monograph Series No. 7, 1959.

2. Alcoholics Anonymous: Alcoholics Anonymous Publishing Co., New York, 1955 (first printing, 1939).

3. Brown, B. S.: What is the government doing about mental health?, Physician's Panorama, October 1965.

4. Giacobini, E., and Salum, I.: Treatment of delirium tremens: A comparative study of different therapeutic methods in 434 cases, Acta Psychiat. Scond., 37: 198-208, 1961.

5. Hayman, M.: A unique day therapy center for psychiatric patients, Ment. Hyg., 41:245-249, 1957.

6. Hayman, M.: The medical practitioner, alcoholism and motivation, Calif. Med., 104:345-351, May 1966.

7. Hayman, M.: Alcoholism: Mechanism and Management, Charles C Thomas Publisher, Springfield, Ill. To be published.

8. Hoffer, A.: Controversial claims for LSD, Canada's Mental Health, p. 31, September-October 1964.

9. Manual on Alcoholism: American Medical Assn., Chicago, 1962 (originally published 1956).

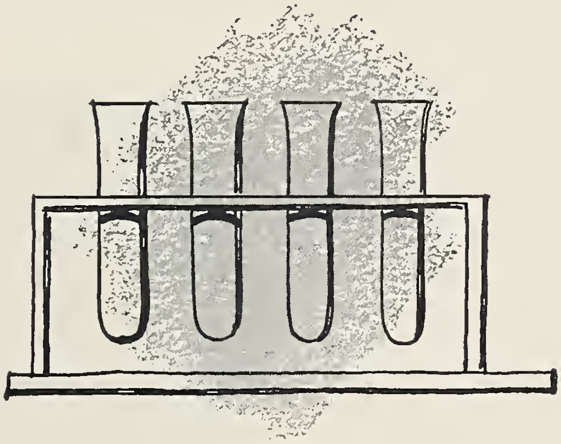
10. Moore, R. A., and Buchanan, T. K.: State hospitals and alcoholism: A nationwide survey of treatment techniques and results, presented at 120th Annual Meeting of American Psychiatric Assn., Los Angeles, California, 1964.

11. New York City Alcoholism Study, National Council on Alcoholism, New York, 1962.

12. Rioch, M. M.: Psychological talent: Reported in Mental Health News, Mental Health Association of Los Angeles County, 8 September 1964.

13. Shaffer, J. W., Freinek, W. R., Wolf, S., Foxwell, N. H., and Kurland, A. A.: A controlled evaluation of chlordiazepoxide (Librium®) in the treatment of convalescing alcoholics, J. Nerv. Ment. Dis., 137:494-507, 1963.

14. Van Dusen, et al.: Lysergic acid treatment of alcoholism, unpublished paper.



CASE REPORTS

Term Twin Pregnancy With Contraceptive Spiral Embedded Behind Placenta

ALBERT F. BARTZ, M.D., *Hayward*

INTRAUTERINE contraceptive devices have been commercially available for several years and have been widely accepted by physicians as well as patients. Although safe and effective, they do not afford complete protection against pregnancy. Among the best known designs are the Lippes loop, the Margulies spiral, the Birnberg bow and the stainless steel ring of Hall. Reports of unintended pregnancy range from 1.1 to 7.5 per hundred woman-years.[1-7]

The spiral produces more side effects than the other devices. With the bow and the stainless steel ring the pregnancy rate is higher than with the other designs.[2] An increase in spontaneous abortion and in ectopic pregnancy is reported in women using intrauterine contraceptive devices.[2,6,7] In no instance has a birth anomaly in a baby born at term been attributed to a plastic device or a stainless steel ring. In the following case a twin pregnancy was carried to term with a spiral in place.

Report of a Case

A 26-year-old white woman who had delivered her fourth child 1 January 1965 was seen for postpartum check-up on 20 February 1965. The uterus was small and non-gravid. An aerosol contraceptive foam was prescribed for use until first postpartum menstruation, which occurred 25 March 1965. On the fifth day of this cycle a Margulies spiral contraceptive device was inserted without difficulty. Uterine spotting and mild cramps persisted for several days. No treatment was necessary.

In May, bleeding and cramping recurred. Two beads of the tailed spiral protruded from the cervix and were excised rather high in the cervical canal. The uterus appeared somewhat soft, and the cervix showed signs of congestion consistent with early pregnancy. On 23 June the patient had low backache and moderate uterine cramps. The tail of the spiral could not be seen and the uterus

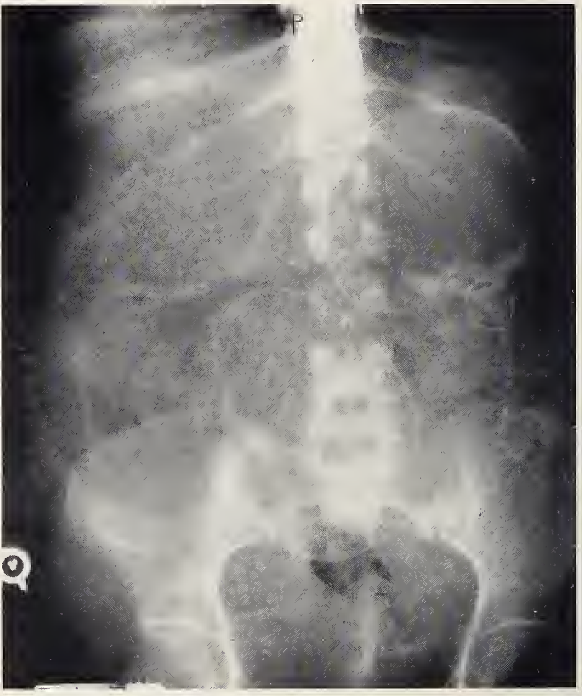


Figure 1.—Plain film of the abdomen showing twin-pregnancy near term with the intrauterine contraceptive device in the left upper quadrant. (Courtesy, Radiology Department, St. Rose Hospital, Hayward.)

Submitted 22 March 1966.

Reprint requests to: 389 Gresel Street, Hayward, California 94544.

was enlarged to a size consistent with 12 weeks of gestation. In October two distinct fetal heart-tones could be heard. An x-ray film taken 2 December 1965 confirmed a twin pregnancy and the spiral was shown in the left upper quadrant of the uterine cavity (Figure 1). On 18 December the patient delivered normal healthy female twins, one weighing 6 pounds 12 ounces and the other 6 pounds. The placenta was in the upper posterolateral portion of the uterus and the spiral was found between the decidua basalis and the maternal surface of the placenta (Figure 2). The membranous septum showed two amnions and two chorions, suggesting double-ovum twins.

Comment

In previously reported cases of term pregnancy with intrauterine contraceptive devices in place, delivery was not complicated by the presence of the device.[4,5] Lehfeldt, Kulka and Liebmann[4] reported an uneventful twin pregnancy with the intrauterine contraceptive device between the amniotic sac and the uterus.

In the present case the anatomical findings indicate that after implantation of the ova the placental villi branched out and spread peripherally, completely covering the intrauterine contraceptive device.

Summary

Pregnancy and birth of dizygotic twins, with a plastic spiral intrauterine contraceptive device in situ throughout gestation, is reported. Only the early antepartum course was complicated by bleeding and cramping. Late pregnancy and delivery were uneventful. The spiral was situated between the cotyledons of the placenta and the decidua basalis.

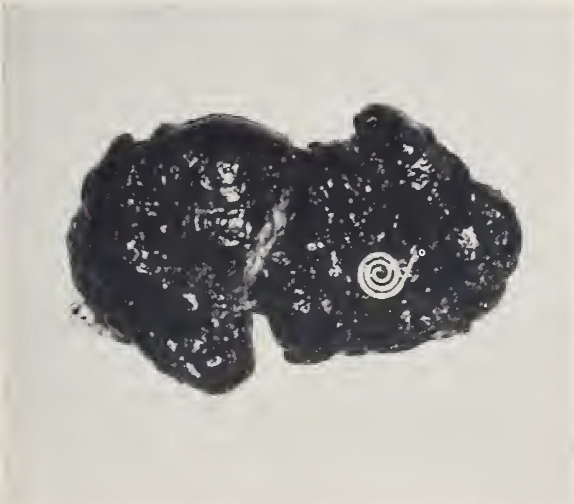


Figure 2.—Maternal surface of placenta with Margulies spiral in situ.

REFERENCES

1. Birnberg, C. H., and Burnhill, M. S.: A new intrauterine contraceptive device, Am. J. Obst. & Gynec., 89: 137, 1 May 1964.
2. Hall, R. E.: A comparative evaluation of intrauterine contraceptive devices, Am. J. Obst. & Gynec., 94:65, 1 January 1966.
3. Lay, C. L.: Intrauterine contraceptive devices, Am. J. Obst. & Gynec., 93:330, 1 October 1965.
4. Lehfeldt, H., Kulka, E. W., and Liebmann, H. G.: Comparative study of intrauterine contraceptive devices, Obst. & Gynec., 26:679, November 1965.
5. Lippes, J.: Contraception with intrauterine plastic loops, Am. J. Obst. & Gynec., 93:1024, 1 December 1965.
6. Tietze, C., and Lewit, S.: Proc. Second Conf. on intrauterine contraceptive devices, Experta Med. International Congress Series N. 86, 1964.
7. Willson, J. R., Ledger, W. J., Bollinger, C. C., and Andros, G. J.: The Margulies intrauterine contraceptive device, Am. J. Obst. & Gynec., 92:62, 1 May 1965.

Congenital Skull Fracture

JAMES M. DUNN, M.D.
ROBERT RASKIND, M.D.
Oakland

FRACTURES of the fetal skull antepartum are generally attributed to traumatic forceps delivery,[4,11] but have been reported to occur during spontaneous labor unassociated with known trauma.* In the case presented here, there was ample radiologic and neurosurgical evidence that a depressed fracture of the fetal skull was approximately three weeks old at the time of delivery. A depressed fracture is more common than a linear one in this situation. It has been suggested that such a depressed fracture results from force exerted against the presenting fetal skull by a prominent sacrum or the symphysis pubis,[2,4,7,10] or that it is caused by pressure from the fetal heel.[2] Some investigators have expressed belief that these depressed areas entail no break in the continuity of bone

---

From the Department of Obstetrics and Gynecology, and the Department of Neurological Surgery, Kaiser Foundation Hospital and The Permanente Medical Group, Oakland.

Submitted 18 April 1966.

Reprint requests to: 280 West MacArthur Boulevard, Oakland, California 94611 (Dr. Dunn).

*Reference Nos. 3, 4, 7, 10, 13.

and hence are not true factors.[3,7] Regardless of the variance in concepts regarding the cause, the standard treatment is surgical elevation.

Report of a Case

A 31-year-old woman with normal obstetrical history had spontaneously delivered two infants, eight and four years before her third pregnancy. The larger infant had weighed 7½ pounds and labor had lasted 2½ hours. During her third pregnancy the patient gained 14 pounds. There were no signs of toxemia or uterine bleeding. Labor started at 2:00 p.m., seven days after the expected date of confinement, with irregular uterine contractions. On examination soon after admission to hospital nothing abnormal was noted. The fetus was in cephalic right occiput anterior presentation at −3 station. The cervix was dilated to 3 cm and fully effaced. Fetal membranes were intact. Uterine contractions continued irregularly. At 6:00 a.m. they were of poor quality and occurring at intervals of 5 to 8 minutes; the cervix was dilated to 3 or 4 cm; the fetal head was still at −3 station. At 8:45 a.m., because contractions were increasingly irregular, 100 mg of meperidine was administered intramuscularly. At approximately 10:00 a.m., abdominal pain suddenly increased. At that time the uterine os was dilated to 7 cm, the fetal head was at −2 station and membranes were intact. Fetal heart tones were slightly irregular. At 10:15 a.m. the pain became more intense; the os was dilated to 8 cm, the fetal head was at −1 station and irregularity of fetal heart tones increased. In the delivery room, paracervical pudendal anesthesia was induced with mepivacaine, 1 per cent.

Amniotomy was performed and a large, fresh blood clot was expelled together with bloody amniotic fluid. The cervical os was fully dilated. The fetal head was at 0 station, in right oblique anterior position, with rather pronounced anterior asynclitism. After amniotomy the fetal heart rate dropped to 100 per minute and continued gradually to decline. Tucker-McLane midforceps were applied with Bill's axis-traction bar. The fetal heart rate was now 50 per minute. Difficulty was encountered in applying the forceps because the sacral promontory projected far into the canal, the fetal head was wedged against it, and asynclitism persisted. Another obstetrician examined the application of the forceps. At 10:52 a.m., after easy traction, a viable male infant weighing 8 pounds, 5 ounces was delivered across an intact perineum. Application of the forceps was again examined and the blades were found to be in satisfactory bimalar position.

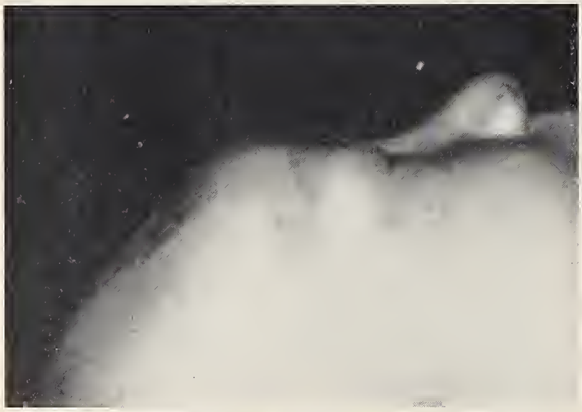


Figure 1.—Preoperative photograph, showing 5×5 cm depression in the right frontoparietal area.

Endotracheal intubation was instituted immediately. The infant responded rapidly: The Apgar score at 1 minute was 7; regular, unassisted respirations were established at two minutes, and at 10 minutes the Apgar score was 10. The placenta, delivered spontaneously at 10:55 a.m., showed signs of old marginal abruptio placentae with areas indicating recent, almost complete, abruptio. The uterus contracted well and bleeding was minimal. On examination an extremely prominent sacrum was found to narrow the anteroposterior diameter of the inlet.

When examined by a pediatrician, immediately after resuscitation, the child was crying lustily and showed no signs of paresis. A 5×5 cm depression in the right frontoparietal area of the skull (Figure 1) was free of edema and discoloration. Roentgen examination (Figure 2) revealed evidence of a depressed fracture in the right frontoparietal region of the skull. Widening of the lambdoidal suture indicated that intracranial pressure had been increased for at least two weeks. A neurosurgical consultant believed that the lesion was a congenital depressed skull fracture.

The next morning the neurosurgeon carried out surgical examination of the area. A 2-cm incision was made over the coronal suture adjacent to the anterior fontanelle on the right side. As the skin was opened careful search was made for old blood and none was found. There was no blood staining of the subgaleal space or pericranium. By subpericranial dissection, the coronal suture was exposed and the dura separated. No blood was found in the extradural space. By means of a blunt elevator, the depressed fragment was restored to normal anatomical position and the wound was closed in layers with silk. Postoperative physical and roentgenologic examinations (Figure 3) revealed normal skull contour.

The postoperative course was uneventful and the infant was discharged in good condition on the eighth day of life. The mother had been discharged in satisfactory condition on the third postpartum day. She had had moderate lumbosacral pain during the puerperium.

Discussion

This fetus showed distress secondary to abruptio placentae; signs of progressive deterioration necessitated expeditious delivery. Midforceps application was carried out on the asynclitic skull. When forceps application was examined by attending obstetricians, before traction was exerted and again after delivery, the blades were properly positioned.

Even though such a concept was inconsistent with the findings, the depressed skull fracture seen immediately upon delivery was first believed to have resulted from obstetrical trauma secondary to forceps application. The neurosurgeon, however, estimated that the fracture was about three weeks old. This estimate was based on two observations: (1) Preoperatively, there was roentgen evidence of widening of the lambdoidal suture, indicating that there had been increased intracranial pressure for at least two weeks; and (2) at the time of operation there was no bleeding and no hematoma. Bleeding is always present at fresh fracture sites; it is within the area of bleeding that the healing process begins, and the progress of this normal response may be used as a guide for approximating the length of time the restorative changes have been present. By the third week there is usually little or no hematoma formation left at the fracture site, and rearrangement of the callus begins to take

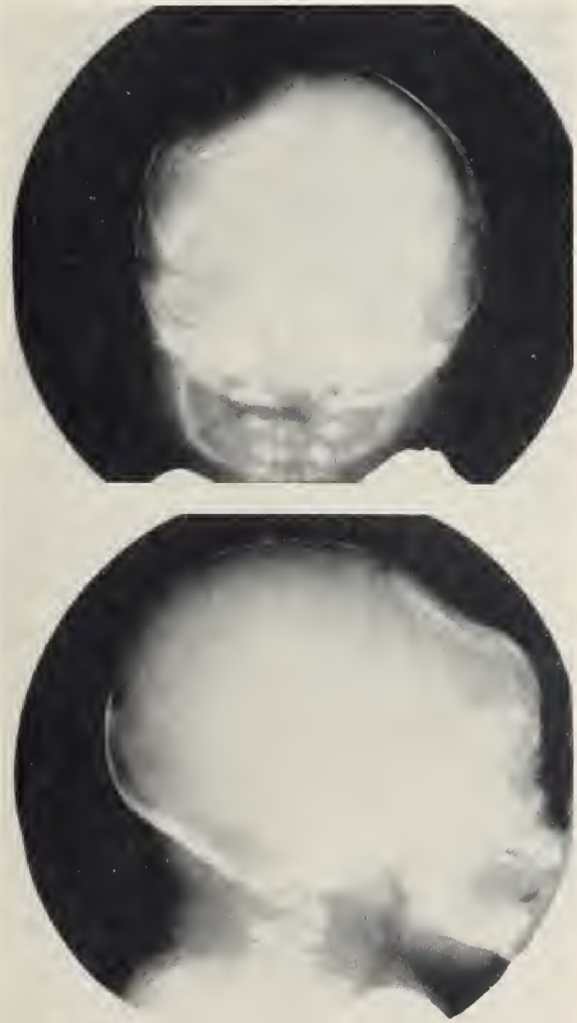


Figure 2.—Preoperative roentgen films, frontal and lateral views, showing the depressed fracture.

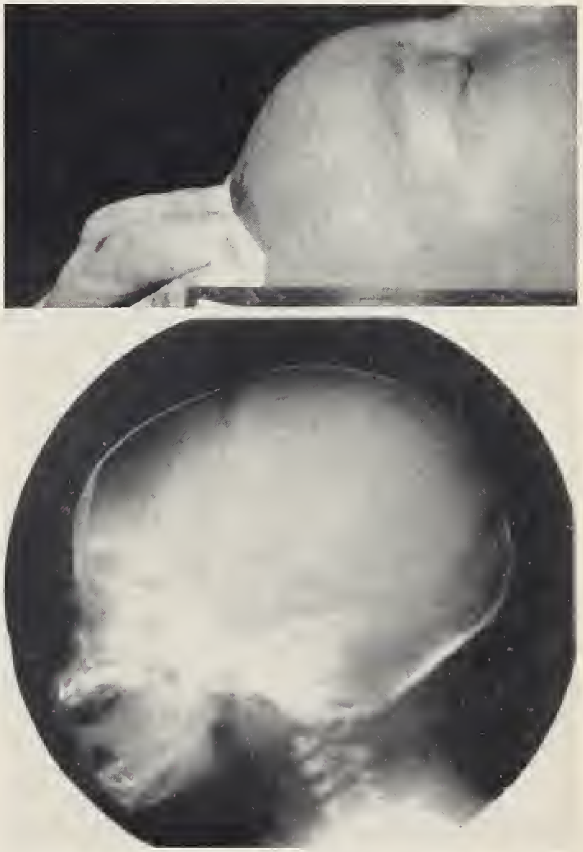


Figure 3.—Postoperative gross appearance and roentgen view showing normal skull contour.

place.[12] The neurosurgeon in the present case successfully elevated the depressed portion of the cranial vault in four previous instances of congenital skull fracture due to intrauterine events.[8]

Penfield and Jasper[6] indicated that the incidence of epileptic seizures resulting from generalized increase in intraventricular pressure differs from that resulting from direct pressure upon the grey matter of the cerebral cortex, hydrocephalus not being *per se* a cause of epilepsy. They expressed the opinion that patients with local compression of the cerebral cortex in one or more areas (as was present in the case described here) seem to be benefited by decompression through elevation of the offending portion or portions of the cranial vault. Both Brock[1] and Munro[5] also stated that operative intervention is indicated for spoon-shaped depressions of the skull, and outlined procedures essentially identical with that used in this case: An appropriate opening is made in the bone, a curved, blunt elevator is introduced between skull and dura, and the depressed segment of bone is restored by gentle pressure to normal anatomical position. Like Brock, we have found simple elevation by this means to be the method of choice. Among more than 30 cases of depressed skull fracture treated by one of us (R. R.)[9] it was necessary in one patient to elevate the fragment the second time, using the same burr hole; and in one other patient, to turn a flap and remove the bone. In our experience, morbidity has been minimal, and mortality zero, following this procedure.

Summary

A fetus showing distress resulting from abruptio placentae was delivered by midforceps applied to the asynclitic skull with satisfactory bimalar placement of the blades. A depressed skull fracture in the right frontoparietal region was first attributed to the forceps, even though the location of the lesion was not consistent with the site of application. Widening of the lambdoidal suture noted roentgenologically indicated increased intracranial pressure had existed for at least two weeks. The depressed fragment was elevated by the neurosurgeon. There was no bleeding at the fracture site, and no hematoma, indicating that the lesion was at least three weeks old.

REFERENCES

1. Brock, S.: Injuries of the Brain and Spinal Cord and Their Coverings, Williams & Wilkins, Baltimore, 1949, p. 14.

2. Caffey, J.: Pediatric X-Ray Diagnosis, 4th ed., Year Book Medical Publishers, Inc., Chicago, 1961, p. 72.

3. Greenhill, J. P.: Obstetrics, 12th ed., W. B. Saunders Co., Philadelphia, 1960, p. 844.

4. McKay, R. J., Jr., and Smith, C. A., in Nelson, W. E., Ed.: Textbook of Pediatrics, 7th ed., W. B. Saunders Co., Philadelphia, 1959, p. 316.

5. Munro, D.: Craniocerebral Injuries; Their Diagnosis and Treatment. Oxford University Press, New York, 1938.

6. Penfield, W., and Jasper, H.: Epilepsy and Functional Anatomy of the Human Brain. Little, Brown & Co., Boston, 1954, p. 321.

7. Potter, E. L.: Pathology of the Fetus and Infant, 2nd ed., Year Book Medical Publishers, Inc., Chicago, 1961, pp. 94-95.

8. Raskind, R.: Neonatal skull fractures, in preparation.

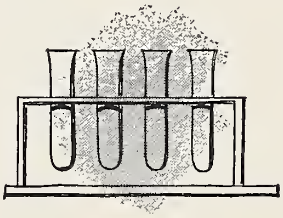
9. Raskind, R.: A technique for elevation of simple bony depressions in infants, in preparation.

10. Reid, D. E.: A Textbook of Obstetrics, W. B. Saunders Co., Philadelphia, 1962, p. 649.

11. Schaffer, A. J.: Diseases of the Newborn, W. B. Saunders Co., Philadelphia, 1960, p. 601.

12. Stowens, D.: Pediatric Pathology, Williams & Wilkins Co., Baltimore, 1959, p. 589.

13. Titus, P.: The Management of Obstetric Difficulties, 3rd ed., C. V. Mosby Co., St. Louis, 1945, p. 877.



MEDICAL STAFF CONFERENCE

Reiter's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. JAMES M. LINDAUER*: The patient is a 22-year-old single male college student who entered the University of California Hospital because of arthritis. At ages 17, 19, and 22 he had episodes of dysuria and urethral discharge of pus. A diagnosis of gonococcal urethritis was made. Treatment with penicillin was administered and the symptoms were relieved. Two months before admission to hospital the patient first noted pain and swelling of the left great toe and left ankle. He had transient pains in the knees, hips, fingers and lower back, and on one occasion in the right temporomandibular joint. During this time, he had intermittent urethral discharge of pus without pain. He denied conjunctivitis, photophobia, skin rash or diarrhea. The remainder of the medical history was unremarkable but his brother was said to have Reiter's syndrome.

On physical examination vital signs were observed to be within normal limits, as were the heart, lungs and abdomen. Slightly raised erythematous lesions with pale central areas were seen on the buccal mucosa. There was loss of lumbar lordosis and tenderness over the lumbar spine was noted. There was a small papule on the glans penis. The ankles were slightly warm, swollen and tender, and pain was evoked on motion of the right hip. On examination of the eyes no evidence was seen of conjunctivitis or uveitis.

Laboratory data are shown in Table 1.

DR. WARREN M. RUSSELL*[1]: The x-ray findings are not particularly striking. In the foot, there was some slight swelling in the first metacarpal phalangeal joint on the left; but no evidence of joint erosion. A lateral view of the right foot showed slight swelling of the soft tissues around the ankle joint, but again there was no evidence of cortical destruction or bone erosion; no spurs were seen and no erosions about the calcaneus so frequently seen in Reiter's syndrome. The sacro-iliac joints were probably normal although there was some suggestion of a slight widening of these joints. A tomogram of the sacro-iliac joints showed some blurring of the joint margins on the right, but these findings were equivocal and could well be within normal limits. A survey of other joints of the spine and hand showed no abnormalities.

DR. LLOYD H. SMITH, JR.*[2]: Being improved on salicylate therapy, the patient was discharged from hospital four days ago and he has returned for presentation this morning. Before presenting him,

TABLE 1.—*Laboratory Data in a Case of Reiter's Syndrome*

Hematocrit—41 per cent
Leukocytes—12,000 per cu mm of blood
Sedimentation rate—31 mm per hour
Urinalysis—within normal limits
Latex fixation test—negative
Creatinine—1.1 mg per 100 ml
Alkaline phosphatase—4 Shinowara-Jones-Reinhart Units (normal 2 to 6 units)
Uric acid—2.1 mg per 100 ml
Lupus Erythematosus preparations—negative
Fluorescent antinuclear globulin test—negative
Anti-streptolysin titer—125 Todd units (normal—less than 166)
Electrocardiogram—within normal limits

---

*Resident in Medicine.

*[1] Assistant Professor of Radiology.

*[2] Professor and Chairman, Department of Medicine.

I would like to introduce our speaker for this morning, Dr. Howard J. Weinberger, who is Associate Clinical Professor of Medicine at U.C.L.A. and unquestionably the leading authority on Reiter's syndrome in the country today. I have asked him to present the patient. (Patient enters.)

DR. HOWARD J. WEINBERGER*[3]: When you had infections in the past, was it definitely proven that those were due to gonorrhea?

Patient: Yes.

Dr. Weinberger: Were cultures taken?

Patient: Yes.

Dr. Weinberger: Did you respond promptly to penicillin?

Patient: Yes.

Dr. Weinberger: Did you have penicillin with this episode?

Patient: No.

Dr. Weinberger: Were cultures taken?

Patient: No.

Dr. Weinberger: Have you had any fever with these attacks?

Patient: None that I have noticed.

Dr. Weinberger: Is there anything which precipitates these attacks?

Patient: Nothing that I know of.

Dr. Weinberger: Where are you having your trouble now?

Patient: Just in my joints—my ankles and lower back.

Dr. Weinberger: Do you awake in the morning feeling stiff?

Patient: Yes. I remain that way all through the day.

Dr. Weinberger: Have you had any rash?

Patient: No, just the redness around my joints.

Dr. Weinberger: Do you have any changes in your nails?

Patient: No. (Patient leaves.)

Dr. Weinberger: I am sorry that Dr. Ephraim Engleman could not be here to discuss this case because this disease really should be called Engleman's disease. It was his report in 1941 in collaboration with Dr. Walter Bauer, the first original report in the American literature, that drew attention to this syndrome. During World War II, many cases involving young men in military service were reported and real interest in the syndrome developed.

This patient's illness is a fairly typical example of Reiter's syndrome. Although he has not had conjunctivitis, he has had urethritis, arthritis, sacro-iliac changes and cutaneous manifestations which characterize the illness.

Reiter, in 1916, believing that the disease was due to a spirochete, introduced the name *spirochetosis arthritica.* That a spirochete was the etiologic agent was not confirmed and the illness has been described under various names by other authors, with emphasis on either the venereal or the diarrheal aspects of the illness. There is no clear explanation of why in certain areas of Europe one sees its onset in association with venereal exposure and in others in association with diarrhea or proven bacillary dysentery. Since the first report in the American literature by Engleman and Bauer, several hundred reports have appeared. The syndrome, although not common, is certainly not rare. The majority of patients described in the literature are young men, usually 20 to 30 years old. Apparently the disease has occurred in male children as young as four years. It is rare in females. Definite precipitating and predisposing factors usually are not recognized, although some observers strongly emphasize the venereal origin. It would appear that many cases are not venereal in origin, particularly those in which the onset is associated with bacillary dysentery. In a group of 15 patients whom I observed, four denied having had sexual intercourse and only two had had previous gonorrhea. However, more recently up to 20 per cent of patients have had proven gonococcal urethritis, which leads to difficulties in separating these two conditions.

In about three-quarters of the patients the onset of illness is concomitant with urethritis. Regardless of the presenting symptom, usually within a period of one to five weeks the entire triad will have evolved. The constitutional symptoms are only mild to moderate in severity. Some patients have had significant loss of weight. Usually patients are febrile in the early stages of the attack. They do not have chills, which tends to separate this disease from gonococcal arthritis. One-third of the patients in the series we observed also had diarrhea and vasomotor changes. The usual attack will subside spontaneously within two to six months. Treatment with antibiotics or corticosteroids has not affected the course of the acute attack.

From the observation of patients over a long term and the many descriptions that have appeared in the literature, a wider clinical spectrum of this illness has evolved. The patients can be divided into three general groups in accordance with differences in clinical course. About 25 per cent of patients will have an acute typical attack of the triad of clinical symptoms and then remain well for a long time. We recently saw a patient who was well for 22 years between the initial attack and the first recurrence. A second group of patients, about half of the total, will have a rather characteristic onset, and then months to years afterward will have repeated attacks involving either the full triad or just arthritis or balinitis alone. Iritis apparently can be one of the manifestations of recurrent activity. Recurrent attacks tend to be less severe than the first ones. There is a third group, made up of about 25 per cent of those who have the disease, whose illness starts atypically and presents a diagnostic problem. For years these patients may have recurrent attacks of urethritis or conjunctivitis or bouts of arthritis resembling infectious arthritis; or they may have two of the three manifestations. Usually, as in the patient presented this morning, one sees urethritis and arthritis rather than conjunctivitis and urethritis. About 75 per cent of the patients will have recurrences and about 65 per cent of the total number will have evidence of mild, continuing activity after the first attack, usually not serious and most commonly manifested by chronic backache. The incidence of the tendency to chronicity and the development of permanent deformities and destructive changes is higher in the group that tends to have recurrent attacks.

---

*[3]Associate Clinical Professor of Medicine, University of California, Los Angeles.

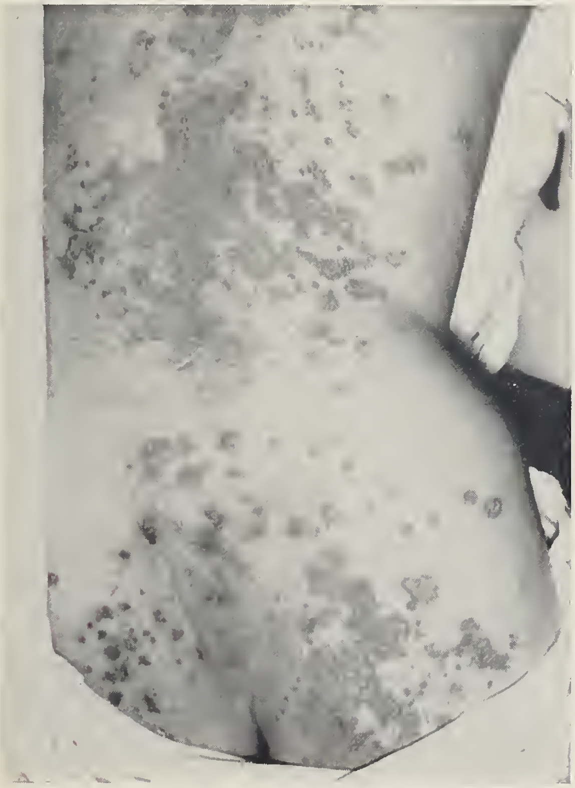


Figure 1.—Hyperkeratotic crusted lesions on trunk tending to be confluent in pressure areas.

The conjunctivitis can be relatively mild and easily overlooked. The patient presented today may have had it without its being recognized by either the patient or the physician. Occasionally the eye involvement, especially when there is iritis or iridocyclitis, is the prominent feature of the attack. In addition to urethritis, prostatitis is extremely common; it occurred in 13 of the 15 patients I observed. In two, prostatic abscesses developed that ruptured spontaneously into the rectum. About one-third of the patients will have so-called abacterial hemorrhagic cystitis, manifested by urinary urgency and frequency, suprapubic pain and so-called abacterial hematuria and pyuria. On cystoscopic examination, diffuse edema of the bladder wall, with membranous sloughs and petechial bleeding, may be seen. At times the edema of the bladder wall may be sufficiently pronounced to cause obstruction of the ureters. If there is serious involvement of the bladder, it may be wise to put catheters into the ureters to promote drainage. Seminal vesiculitis has been seen, but not epididymitis, which occurs in gonococcal infection.

The cutaneous manifestations have not been emphasized sufficiently in the past. The cutaneous manifestations are more striking, probably are seen more often and are more specific in nature than the ocular findings (Figure 1). Sometimes the only change may be slight alteration in the nail beds on one or two fingers; there may be brownish discoloration, or accumulation of waxy material under the free end of the nail. Often, there is more striking alteration in the nails resembling that of fungous infection, but cultures uniformly are negative. The nail involvement can be very severe at times and a cast of the end of the finger may slough off in healing. This severe skin involvement is often called keratosis blenorrhagica and, as I will emphasize later, probably all the cases of keratosis blenorrhagica are manifestations of Reiter's syndrome rather than the result of a sensitivity to gonorrheal infection. This extensive cutaneous involvement usually heals completely without scar formation. The big toe is frequently involved by a

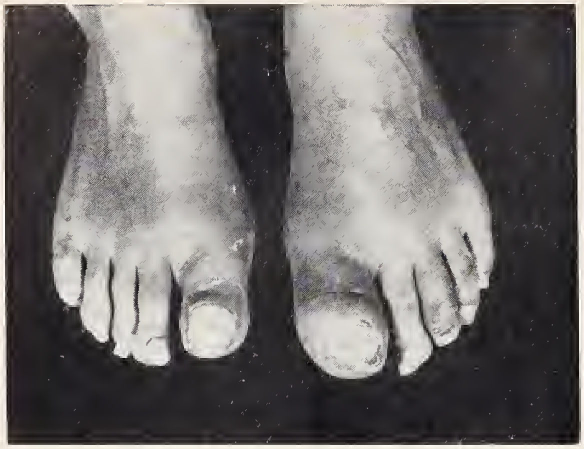


Figure 2.—Nail alterations in Reiter's syndrome showing discoloration, loosening of the free ends, and merging of subungual and cutaneous keratoses, the latter giving rise to "sausage toe" appearance.

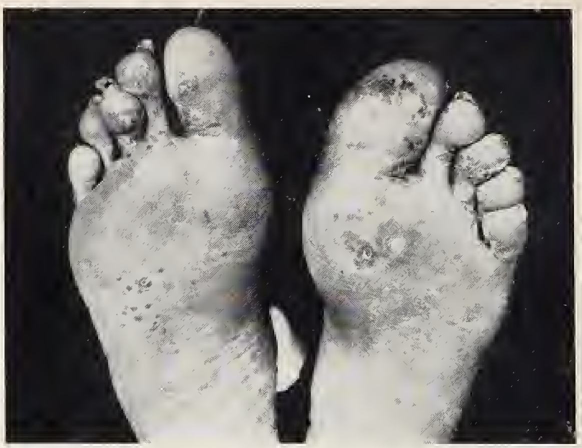


Figure 4.—Discrete and confluent hyperkeratotic lesions on soles of feet with associated nail alterations. (From Weinberger, H. J.: Reiter's syndrome—Clinical and pathologic observations, Medicine, 41: February 1962. Reprinted with permission of publisher, Williams & Wilkins Co., Baltimore, Md.)

lesion that the English call "sausage toe" (Figure 2). It resembles paronychia with a fungous infection of the nails, but this results from a merging of many subungual and cutaneous keratotic formations.

The penile lesions are often overlooked because they may be minimal or nondescript. When there is a discharge of secretion from the urethra, the usual tendency has been to attribute the skin irritation to the discharge; but this is not really the case. There is a very specific penile lesion, consisting initially of umbilicated, keratotic papules. These may be grouped around the meatus and may extend into the anterior urethra (Figure 3). In uncircumcised persons these papules are not as keratotic, and erosion of grouped papules occurs, giving rise to the lesion called balanitis circinata (Figure 3). The appearance of the cutaneous lesion is determined in part by its location. Sometimes the cutaneous lesions are not on the glans but occur at the base of the shaft or in the groin or scrotum.

On the foot, the earliest lesion may be one or two macules that have a yellow center and an erythematous border and appear relatively non-

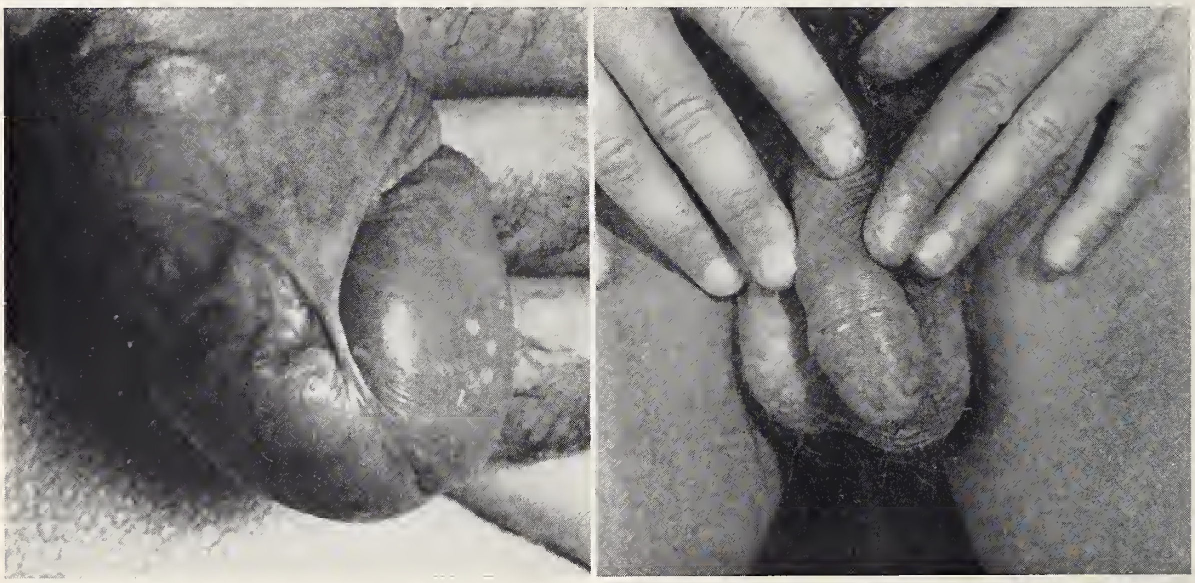


Figure 3.—*Left,* Discrete moist eroded papules on glans penis. *Right,* Balanitis circinata lesion on glans penis. (From Weinberger, H. J.: Reiter's syndrome—Clinical and pathologic observations, Medicine, 41: February 1962. Reprinted with permission of publisher, Williams & Wilkins Co.. Baltimore, Md.)

specific. Usually more of these appear as time goes on. I have followed the evolution of these lesions and have observed that the thick horny plaques on the soles of the feet result from the coalescence of the isolated keratotic papules (Figure 4). The lesions resemble those of psoriasis. There seems to be a relationship between psoriasis and Reiter's syndrome and the cutaneous lesions of keratosis blenorrhagica. The lesions on the hands resemble those on the feet. Some excellent dermatologists have told me that it is difficult to differentiate clinically between pustular psoriasis, the lesions of Reiter's syndrome and keratosis blenorrhagica. Oral mucous membrane lesions occur as erosions and scattered papules. They are often seen in association with the penile lesions. Eighty per cent of patients will have lesions of the mucous membrane, the penis, the skin or the nails, occurring independently or together. At times, there may be diffuse erythema of the tongue with considerable inflammatory reaction.

The histological appearance of a single papule on the glans penis shows parakeratosis, some acanthosis, lysis of the superficial prickle cell layers, development of the so-called micro-abscesses, elongation of the rete pegs and an inflammatory reaction (Figure 5). The appearance is somewhat different on the foot, where there is more keratosis, but it is essentially the same kind of reaction. A lesion on the glans penis that is extremely moist may be somewhat different from the others, lacking the keratotic layer but having the micro-abscesses, the thickening of the stratum corium, the clubbing and the inflammatory reaction. The appearance of this lesion is similar to that of an oral mucous membrane lesion (Figure 6). It is the same kind of reaction, consisting of micro-abscesses, acanthosis and inflammatory cell infiltration with venular plugging with leukocytes. Under higher power, one sees more clearly this rather specific lesion which closely resembles psoriasis. The problem is that these lesions resemble psoriasis grossly and histopathologically but psoriasis is not supposed to involve mucous membranes. If it really can, then simultaneous involvement of the skin and the mucous membranes in the urethra, the mouth and the eyes could be an explanation for this syndrome. I have seen patients who had typical Reiter's syndrome with cutaneous lesions and subsequently had chronic psoriasis. A few others who had psoriasis initially later had Reiter's syndrome. There are papers in the literature now describing the coincidental occurrence of lesions of Reiter's syndrome, keratosis blenorrhagica and pustular psoriasis. The relationship between these conditions requires further definition.

The articular involvement is the most prominent feature of the attack. It may be monoarticular but most commonly is polyarticular and very often symmetrical. It resembles infectious arthritis in the suddenness of onset, in the tendency to migration in the initial phases, and in the degree of heat, pain and tenderness in the involved joints. The weight-bearing joints are very commonly affected. The joint involvement may be remarkably symmetrical. This suggests to me the possibility that something which is circulating is producing sym-

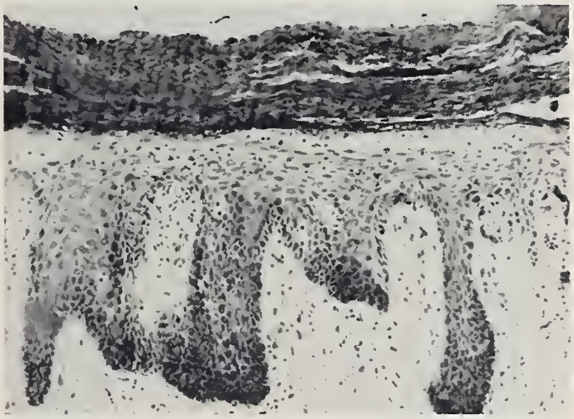


Figure 5.—Skin biopsy showing hyperkeratosis, parakeratosis, acanthosis, elongation of rete pegs, micro-abscesses, and chronic inflammatory cell infiltration. (×105). (From Weinberger, H. J.: Reiter's syndrome—Clinical and pathologic observations, Medicine, 41: February 1962. Reprinted with permission of publisher, Williams & Wilkins Co., Baltimore, Md.)

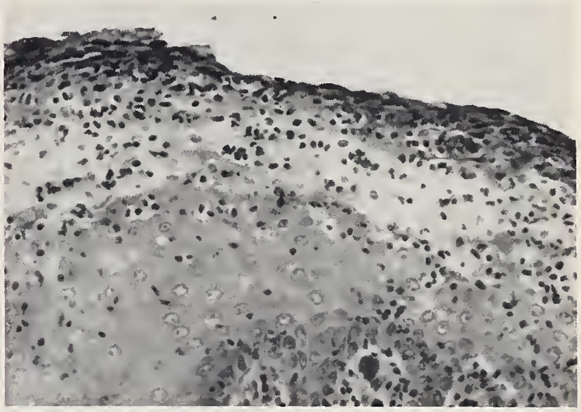


Figure 6.—Oral mucous membrane lesion showing micro-abscess in addition to other alterations seen in skin biopsy. (×480). (From Weinberger, H. J.: Reiter's syndrome—Clinical and pathologic observations, Medicine, 41: February 1962. Reprinted with permission of publisher, Williams & Wilkins Co., Baltimore, Md.)

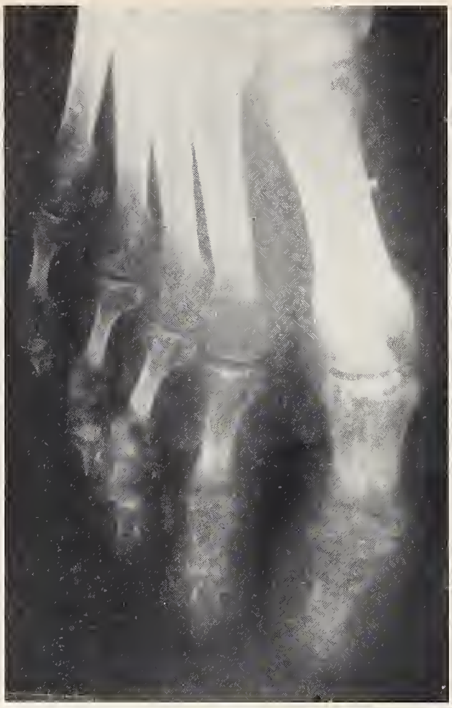


Figure 7.—Spotty demineralization involving subchondral areas suggestive of infectious arthritis or Sudeck's atrophy. (From Weinberger, H. J.: Reiter's syndrome—Clinical and pathologic observations, Medicine, 41: February 1962. Reprinted with permission of publisher, Williams & Wilkins Co., Baltimore, Md.)

metrical areas of involvement rather than an infectious process which usually is not symmetrical. Synovial effusions may be present with fluid findings somewhere between those of a subacute infectious process and rheumatoid arthritis. These consist of elevation of the total leukocyte count, an increased percentage of polymorphonuclear cells and slight widening of the glucose difference between the serum and the synovial fluid. The mucin content is lessened and qualitatively the mucin is usually poor. Symmetrically involved joints may show widely divergent cell counts, from 2,900 per cu mm in one knee to 52,000 per cu mm in the other. Improvement in the leukocyte cell count, lowering of the percentage of polymorphonuclear forms, lowering of the sugar difference and improvement in the character of the mucin may herald remission before it is obvious clinically.

The roentgenographic changes are very important and of great interest. Usually one may see only subchondral atrophy or minimal changes, as in the patient presented today. Not uncommonly one sees a peculiar kind of moth-eaten osteoporosis with flecky decalcification that is not necessarily all subchondral (Figure 7). The radiographic alterations have a great tendency for reversibility, which contrasts with the changes in rheumatoid arthritis. Rarely, destructive changes with narrowing and fusion of the joint spaces occur, but most patients recover completely. Periosteal changes are very striking about the ankle and the heel, which explains the pain in the heel in this disease (Figure 8). At times it is necessary in some patients who have persistent pain in the heel to remove bursal swellings in this area. The pain is not due to the spur but to the inflammatory reaction.

The first patient that Engleman and Bauer saw in 1940 had had several subsequent attacks when he came under my care in 1946 because of backache. Early changes in sacro-iliac joints were noted, consisting of sclerosis and some narrowing and irregularity. Over a three-year period, the sacro-iliac joints became fused. This is the first time that I became aware that sacro-iliac changes occur in this disease. Subsequently, they have been described in up to 30 to 40 per cent of patients. Dr. Good in Ann Arbor has expressed the belief that with long follow-up it will be found that 50 per cent of patients have these changes. It is interesting that these changes may be present early in the course of the illness, as in the case at hand. I have seen a number of patients who had sacro-iliac involvement at the time of onset of the triad. I also have seen patients who had spondylitis at the time of discharge from the military service and later had Reiter's syndrome. In a fair number of

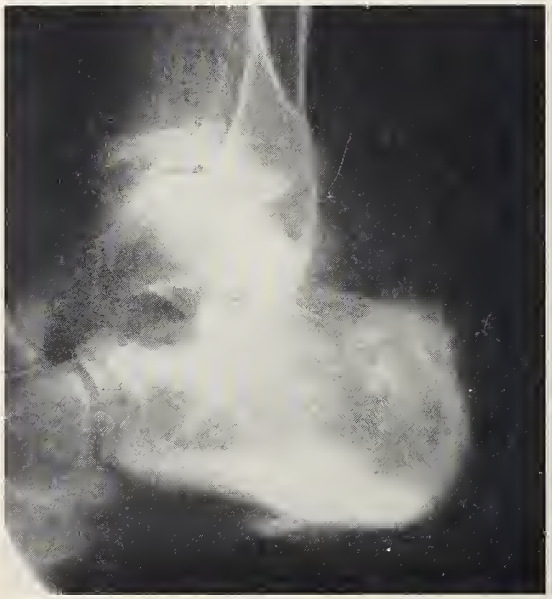


Figure 8.—Periostitis around ankle joint and especially the calcaneus, fairly characteristic of Reiter's syndrome.

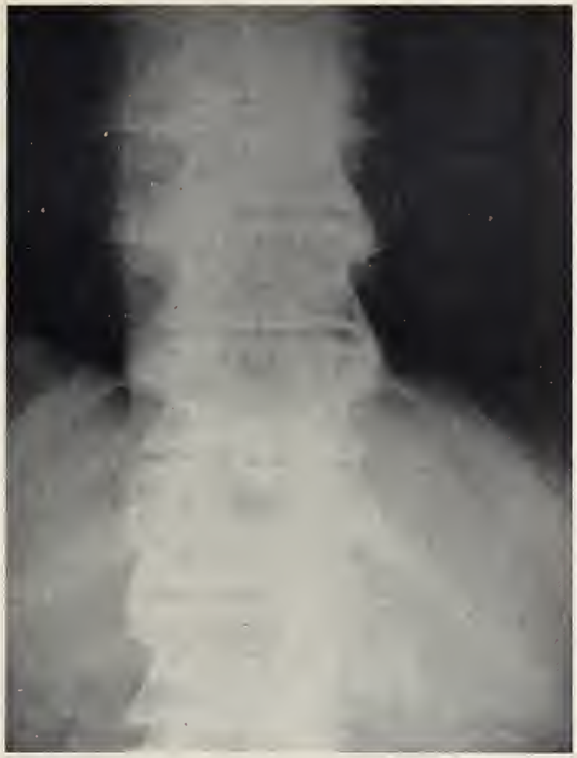


Figure 9.—Asymmetrical lateral calcifications arising from the diaphyseal portion of vertebral bodies, resembling a comma, being broader at the base and tapering somewhat.

patients with Reiter's syndrome spondylitis will develop, but there are certain features that are somewhat different from those of ordinary rheumatoid spondylitis.

There is an asymmetry in the involvement and there is the comma sign that occurs in Reiter's syndrome. The calcification does not follow the contour of the paraspinal ligament but arises from the diaphyseal portion of the body of the vertebra and extends upward or downward to join that arising from the adjacent vertebra (Figure 9). This is also seen in psoriatic spondylitis; and it is different from the ligamentous calcification seen in the spondylitis of ulcerative colitis, regional enteritis, Whipple's disease, and rheumatoid spondylitis. That Reiter's syndrome and psoriatic spondylitis resemble one another radiologically again suggests a relationship between psoriatic arthritis and Reiter's syndrome.

In biopsy specimens of the synovial membrane excised in the acute phase, vascular congestion and polymorphonuclear cell infiltration within the membrane can be seen. There is also edema and extravasation of blood. In the subacute stage, the inflammatory reaction is limited to the superficial portions of the synovial membrane and more of the cells present are mononuclear. The microscopic appearance of tissue excised from a chronically-involved joint is comparable to that seen in rheumatoid arthritis, with large lymphoid follicles, perivascular cuffing, hypertrophy, hyperplasia of the synovial membrane lining cells, plasma cells and lymphocytic infiltration.

Heart involvement also occurs in Reiter's syndrome. Occasionally, patients have been considered to have rheumatic fever. One of the first patients I saw had aortic insufficiency, and more recently other investigators have reported two or three instances of aortic insufficiency in Reiter's syndrome. Pericarditis is not uncommon and electrocardiographic changes occur in half of the patients.

Laboratory findings are not too helpful. Leukocytosis, pyuria and elevated sedimentation rates are seen. Positive reaction to latex tests for the rheumatoid factor have been seen in some patients, although in most cases this test will be negative. The serum proteins are not particularly altered.

Routine cultures are not helpful, but they should be done. I have not found any evidence for bacillary dysentery as a causal agent. Frei tests and dark field examinations have been negative. In my experience the only suggestive evidence for a possible etiologic agent has been the identification, in the urinary sediment and joint fluid, of what were called PPLO, or pleuropneumonia-like organisms but are now called mycoplasma. These organisms have fastidious growth requirements; the individual organisms are submicroscopic and are filterable. The total colony often is no larger than a red cell. We have found these organisms in the genito-urinary tract in approximately 40 per cent of patients with Reiter's syndrome. Sporadic reports of isolations of these organisms in synovial fluid have appeared. The disturbing thing has been the finding of these organisms in so-called normal persons. They were found in 36 per cent of a group of sailors being discharged from the Chelsea Naval Hospital. But when these sailors were studied more carefully, it was found that there was a 65 per cent incidence in those with genito-urinary infections. We found these organisms in the presence of nonspecific urethritis or prostatitis in 172 patients, and in 52 they were present in pure culture. In hemorrhagic cystitis they were found in pure culture in

20 of 25 cases, although some of the patients did not have Reiter's syndrome. In one case these organisms were recovered from a kidney that was surgically removed because of pyelonephritis. Since the Eaton agent has been described and recognized as a mycoplasma, it is now considered likely that these organisms can be pathogenic. Rheumatologists have become very interested in these organisms since Bartholomew recently reported isolation of mycoplasma by tissue culture techniques in rheumatoid arthritis and lupus erythematosus. Pleuropneumonia-like organisms, or mycoplasma, are arthrotropic in animals and are associated with joint disease in rats, swine, cattle and pigs.

The cause of Reiter's syndrome remains uncertain. There are interesting relationships between psoriasis and psoriatic arthritis and Reiter's syndrome as well as between rheumatoid spondylitis and Reiter's syndrome.

There is strong suggestion that in some instances it is an infectious disease, possibly venereal, although this is still controversial. It is possible that various infectious agents may somehow trigger an immunological mechanism. In this way, some of the so-called auto-immune diseases may be related to infectious agents. In any event study of patients with Reiter's syndrome may yield some clues to the mechanisms that are involved in an acute reversible arthritis that at times becomes chronic and has manifestations resembling rheumatoid arthritis and psoriatic arthritis.

DR. SMITH: We have heard a masterful exposition of the clinical manifestations of Reiter's syndrome from a man who has perhaps contributed more to the delineation of this syndrome than anyone else in the country. Dr. Weinberger, have you had previous experience with a positive family history or sibship involvement .such as there seemed to be in today's case?

DR. WEINBERGER: This is unusual. I know of only one other such instance. Only rarely do patients have a positive family history for rheumatoid arthritis or psoriasis. However, the concept of familial aggregation in connective tissue diseases has been challenged recently, casting some doubt on the possibility that the occurrence of these diseases is genetically influenced.

EDITOR'S NOTE: Following discharge from the hospital, the patient continued to have pain in the left ankle and foot. He was treated with tetracycline with some subjective improvement. He denied any skin lesions. When last seen in the Outpatient Clinic, he had slight tenderness over the left lateral malleolus and left first metatarsal phalangeal joint, without swelling or redness.

REITER'S SYNDROME
No Recent Summaries in the Literature

Editor
DWIGHT L. WILBUR, M.D.

Assistant to the Editor
ROBERT F. EDWARDS

For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MacLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

California
Medicine

EDITORIAL

Hemolytic Disease of the Newborn

Elsewhere in this issue appears the first of a series of papers concerned with a recently completed study of hemolytic disease of the newborn (HDN) in California. This study has been one of the ongoing projects of the Committee on Maternal and Child Care of the California Medical Association, in conjunction with the California State Department of Public Health, and is essentially an extension of the reports on maternal mortality which have been the major activity of this collaboration for the past several years.

The present study is unique in that it has assayed every HDN death occurring in California over a two and a half year period, involving every part of the state, every type of hospital, every economic class, every ethnic and social group and every level of medical care available, as concerned with this disease. The active participants numbered in the hundreds; the review committees alone included, at one time or another, general practitioners, obstetricians, pediatricians, anesthesiologists, pathologists, hematologists and public health physicians. Also involved were hospital administrators, house officers, nurses, laboratory technicians, blood bank personnel and social service staffs. To the credit of all concerned it must be documented that cooperation was rendered most willingly, and was complete in all respects.

The results of the study will be utilized in the continuing medical education activities of the CMA and the State Department of Public Health. Already one panel discussion and a scientific exhibit have been presented at the annual CMA session. Plans for further use of the study findings include additional papers on selected aspects of the study (such as first infant involvement), continued postgraduate education in HDN at state, county and local hospital levels, and lay education through CMA *Health Tips* and other media.

It is hoped that the study will focus the attention of physicians, hospitals and paramedical facilities not only on hemolytic disease of the newborn, but also on the general problems of antenatal care, resources and responsibilities of hospitals and hospital facilities, availability of consultative services, role of teaching hospitals, medical staff interrelationships, and staff committee functions and responsibilities in general hospitals.

It must be emphasized and reemphasized that the evaluation of possible "preventability" or "avoidability" in this study was based upon assessment against the absolutely ideal level of management. This was a condition of the study; it was not intended to set punitive or accusative standards. It is acknowledged that the perfect ideal cannot always be attained, but in efforts to lower infant mortality and morbidity we all are charged with seeking the ideal.

Keith P. Russell, M.D.
Chairman, Committee on
Maternal and Child Care
California Medical Association

California Medical Association

NOTICES AND REPORTS

Wilbur Reelected AMA Trustee

At the meeting of the American Medical Association in June, Dr. Dwight L. Wilbur was reelected to the Board of Trustees for a term ending in 1969. His name was put into nomination by Dr. Samuel R. Sherman with the following speech:

"The office of Trustee of the American Medical Association represents to all of us the ultimate attainment within organized medicine of the opportunity for a member of this association to serve for a potential of nine years for the best interests of American medicine and the American public—our patients. Initial selection and reelection to that office must be based in considerations of ability, stability, performance, integrity, stature and demonstration of responsibility.

"Dwight L. Wilbur of San Francisco has well demonstrated all of these characteristics and qualifications since he first served this House as a delegate starting in 1941 and later as a Trustee beginning in 1963. He has further continually distinguished himself in the medical organization of his home state by serving as Editor of California Medicine, the official journal of the California Medical Association, and as a member of the Council of that association.

"He has been honored by the American College of Physicians through election to the presidency of that eminent body in 1959, and then designation as a Master of the College.

"Dwight L. Wilbur's performance for the past three years as a Trustee has been highlighted by many productive and constructive contributions to the entire association.

"It is again my assigned function to nominate this dedicated and able physician to serve on the Board of Trustees to succeed himself for a second term. I do this with a feeling of deep pride and great personal pleasure."

Reporting of Venereal Disease

At the annual meeting of the California Medical Association in March the House of Delegates passed a resolution dealing with the reporting of venereal disease to the Department of Public Health and recommended that publications of the CMA remind physicians of the legal requirements and their responsibilities in this regard.

The resolution was adopted as follows:

"Whereas, the alarming increase in venereal disease incidence among teenagers and young adults has made V.D. California's most common communicable disease; now, therefore, be it

Resolved: That physicians be reminded that reporting of cases and permitting confidential interviews of patients by public health personnel are essential in the control of venereal disease. Performance of these services, as well as being required by law, is the physician's duty and responsibility."

In Memoriam

Argens, Richard, Imola. Died 23 June 1966 in Napa, aged 64. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1928. Licensed in California in 1937. Doctor Argens was an associate member of the Napa County Medical Society.

✣

Badertscher, Victor A., Dinuba. Died 4 July 1966, in Dinuba, aged 58. Graduate of Western Reserve University of Medicine, Cleveland, Ohio, 1933. Licensed in California in 1941. Doctor Badertscher was a member of the Tulare County Medical Society.

✣

Becker, Harry F., Van Nuys. Died 12 June 1966, in Van Nuys, aged 70, of cancer. Graduate of Rush Medical College, Chicago, Illinois, 1922. Licensed in California in 1922. Doctor Becker was a member of the Los Angeles County Medical Association.

✣

Brown, F. Earl, Los Angeles. Died 28 June 1966, in Los Angeles, aged 88, of bilateral bronchopneumonia. Graduate of Columbia University College of Physicians and Surgeons, New York, New York, 1908. Licensed in California in 1908. Doctor Brown was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Carlson, Albert Steen, Ontario. Died 7 June 1966, in Ontario, aged 55. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Carlson was a member of the San Bernardino County Medical Society.

✣

Edmond, Julian, Jr., Modesto. Died 19 June 1966, in Modesto, aged 56. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1939. Doctor Edmond was a member of the Stanislaus County Medical Society.

✣

Fischer, Siegfried, San Francisco. Died 30 June 1966, in San Francisco, aged 75. Graduate of Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia, Germany, 1917. Licensed in California in 1941. Doctor Fischer was a member of the San Francisco Medical Society.

✣

Fluhmann, C. Frederic, San Francisco. Died 12 June 1966, in San Francisco, aged 67. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1922. Licensed in California in 1926. Doctor Fluhmann was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Hawkins, William John, Arcadia. Died 7 June 1966, in Altadena, aged 56, of ventricular fibrillation. Graduate of Rush Medical College, Chicago, Illinois, 1939. Licensed in California in 1940. Doctor Hawkins was a member of the Los Angeles County Medical Association.

✣

Herzog, Paul, Tarzana. Died 29 June 1966, in Los Angeles, aged 55, of chronic hepatitis with cirrhosis. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1946. Doctor Herzog was a member of the Los Angeles County Medical Association.

✣

Jablonski, John J., San Bernardino. Died 9 April 1966, in San Bernardino, aged 61, of carcinoma of the colon. Graduate of Hahnemann Medical College and Hospital of Philadelphia, Pennsylvania, 1933. Licensed in California in 1954. Doctor Jablonski was a member of the San Bernardino County Medical Society.

✣

Layman, John D., Pasadena. Died 19 June 1966, in Pasadena, aged 62, of cancer of the bladder, metastases. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Layman was a member of the Los Angeles County Medical Association.

✣

Lutz, Gustav A., Glendale. Died 23 June 1966, in Glendale, aged 79, of thrombosis basilar artery. Graduate of The Hahnemann Medical College and Hospital, Chicago, Illinois, 1912. Licensed in California in 1923. Doctor Lutz was a member of the Los Angeles County Medical Association.

✣

Merrill, Harry Palmer, Los Angeles. Died 30 June 1966, in Los Angeles, aged 78, of perforated ulcer with hemorrhage. Graduate of Rush Medical College, Chicago, Illinois, 1913. Licensed in California in 1916. Doctor Merrill was a member of the Los Angeles County Medical Association.

✣

Oddo, Nicholas Vincent, Long Beach. Died 10 June 1966, in San Francisco, aged 50. Graduate of Philadelphia College of Osteopathy, 1944. Licensed in California in 1944. M.D. degree from California College of Medicine, 1962. Doctor Oddo was a member of the Los Angeles County Medical Association.

✣

Shepardson, Dwight Emerson, Redwood City. Died 13 February 1966, aged 72, of heart disease. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1921. Licensed in California in 1921. Doctor Shepardson was a member of the San Francisco Medical Society.

✣

Trainor, Romaine R., San Diego. Died 5 July 1966, in San Diego, aged 52, of heart disease. Graduate of the University of Colorado School of Medicine, Denver, 1945. Licensed in California in 1946. Doctor Trainor was an associate member of the San Diego County Medical Society.

Plan to Attend

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS PLUS THREE GENERAL MEETINGS ON THE SUBJECT:

ADVANCES IN DIAGNOSTIC TECHNIQUE

Capability • Reliability • Integration

SECOND CALL FOR
- *Scientific Papers*
- *Medical Motion Pictures*
- *Scientific Exhibits*

★ **If you have a paper** you'd like to present to your colleagues during their section meeting . . . write today to your section secretary (names and addresses of scientific section officers may be found on page 6, Advertising Section of *California Medicine*). Presentations are not limited to Advances in Diagnostic Technique.

★ **If you have a motion picture or exhibit** . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

PLANS FOR THE 1967 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

WHAT GOES ON

What Goes On, a new physician's guide to continuing education in California and Hawaii, will be published nine times each year and sent to each physician in California and Hawaii beginning with the September issue, due on the physician's desk in mid-August.

Published under the auspices of the Committee on Continuing Medical Education of CMA, Donald W. Petit, M.D., Chairman, the new pocket-size bulletin will present in greater detail a chronological account of all medical postgraduate courses, meetings and continuing education opportunities for the coming month. **What Goes On** will also contain listings of future events. Deadline for **What Goes On** information is two months preceding publication.

The **What Goes On** office will also make available, upon request, information as to time, place and subject of all future activities three years in advance.

REQUEST FOR LISTING OF CONTINUING MEDICAL EDUCATION COURSES, PROGRAMS AND MEETINGS IN "WHAT GOES ON" AND "MEDICAL DATES BULLETIN"

(deadline: **fifth** of preceding month)

From: ______________________ ______________________
(Organization) (Address)

Name of Program or Meeting______________________________________

______________ ______________ ______________
(Date(s)) (Time) (Place)

Principal Subject(s)______________________________________

Principal Speaker(s)______________________________________

Brief Description______________________________________

____

____
(Please forward program to CMA when available)

No. of hours of instruction______________ Fee, if any______________

Advance registration required Yes________ No________

Invitations extended to:______________ Maximum registration______________
(Field or Specialty)

Contact for information:______________________________________
(Name and Title)

____
(Address)

If annual, give dates for:______________ ______________ ______________
(Next year) (Second year) (Third year)

☐ Check here if you would like to receive information on other continuing medical education meetings or programs scheduled at the same time, on the same subject or at the same location.

PUBLIC HEALTH REPORT

LESTER R. BRESLOW, M.D.
Director of Public Health

A Measles Immunization Campaign

An intensive measles immunization campaign was conducted in Imperial County last April to control an epidemic of rubeola. Several features of this campaign were unusual: the rapid planning of the campaign, the cooperative effort of local, state and federal personnel, the support given by the community to the effort and the utilization of Hypospray Jet Injector Guns deserve special notice.

Beginning in mid-February, Imperial County began to experience a rise in the number of cases of rubeola reported. This trend continued into March and with decided acceleration by mid-month. Cases were being reported at a rate about three times that of the previous two years. Because of the sharp rise in the number of cases and the continuing acceleration of the rate of incidence, the county health officer felt it advisable to conduct an intensive measles immunization campaign in an effort to control the epidemic.

Although Imperial County had applied for funds through the Vaccination Assistance Act, the application had not yet received final approval and therefore, vaccine could not be obtained through this channel promptly enough to be of use in controlling the epidemic. However, consultation with the Communicable Disease Center of the United States Public Health Service revealed that there was a limited amount of Philips-Roxanne live virus measles vaccine (Edmonston Strain) which could be made immediately available for a special study. The specific objective of the study would be to see if intensive immunization of children in the early school grades would assist in controlling the epidemic. Immunizations would also be offered to children of preschool age, however.

The Imperial County Medical Society was advised of the proposed activity and gave its support and cooperation.

Planning for the campaign proceeded very rapidly. It was determined that school children from kindergarten through the third grade who had not previously received measles vaccine or had had the disease would be offered vaccine in all of the county's public and parochial elementary schools over a three-day period. Clinics would be conducted on a fourth day primarily for preschool children. It was also determined to use Hypospray Jet Injector Guns so that the large number of immunizations could be accomplished within the desired time.

Before the immunization sessions were begun, a telephone survey of 200 families was carried out to determine susceptibility levels of children up to age 11 years, and to assess the incidence of the disease. It was estimated on the basis of survey information that there were approximately 10,000 susceptible children in the age group of concern throughout the county. This estimate was later considered to be somewhat high because of the large number of children who had just recently had rubeola during the course of the epidemic.

Consent forms were distributed through the schools explaining to the parents that the immunizations would be given at the schools and inquiring whether the child had already received measles immunization or had already had the disease. The response was very gratifying; approximately 90 per cent of the children returned the consent forms. Many of these forms, of course, indicated that the child was already immune. The school nurses reviewed the forms and only susceptible children were scheduled for the immunization sessions.

The campaign was publicized through mass media, and posters and handbills were distributed.

Because of the large Spanish-speaking population in the county, materials were prepared in Spanish as well as English. Personal contacts were also made in areas where immunity levels were suspected to be low.

The actual immunization sessions were conducted by three teams of five persons each. Team personnel was recruited from Public Health Service Communicable Disease Center, from the California Vaccination Assistance Program and from the Imperial County Health Department.

A total of 7,182 immunizations were given during the four days of clinic (4,052 to school children and 3,135 to preschool children. It is estimated that 85 to 90 per cent of the susceptible school-age children and approximately 50 per cent of the preschool age susceptibles were immunized.

Of particular interest in the campaign was the use of Hypospray Jet Injector Guns. These guns demonstrated their usefulness and versatility. Two types of guns were used. The electric models were used to inject the vaccine, and the smaller hand models were used for the gamma-globulin which was also given to each child. The use of the guns was learned quickly by personnel who had not previously used them, and the speed of injection made the campaign feasible.

Of particular note was the great acceptance of the technique by the children. There was little evidence of fear or pain. Most of the children seemed, in fact, to enjoy the experience and were very interested in the equipment.

Careful inquiry was made into the occurrence of post-immunization reactions both by telephone survey and by personal contact with the physicians in the county. No mothers called specifically because of concern regarding a reaction. A small number did call the health department to inquire whether the slight fever or rash that they noted in the child was the result of the immunization. A telephone survey determined that as many as 85 to 90 per cent had some mild fever and 15 to 20 per cent had a slight rash. The mothers reported, however, that despite these reactions the children did not seem ill, and the mothers were not especially concerned. Information had been given to each of the mothers at the clinics that some rise in temperature and perhaps rash could be expected following the vaccination. This seemed to have helped a great deal in preventing any alarm or unusual concern.

The effect of the immunization campaign upon the spread of the epidemic was considerable. It had been postulated that the major spread of the epidemic was through the children in the early school grades and that, therefore, intensive immunization of these children could possibly abort the epidemic. This seems to have occurred. During the first week following the campaign the incidence of cases continued to rise. Since that time, however, it has shown a sharp downward trend. During the first week of June, for example, only five cases were reported. School absenteeism also declined sharply.

In summary, it is felt that the intensive measles immunization campaign in Imperial County during April 1966 substantially achieved its major objective of controlling an epidemic of rubeola. One can estimate that had the epidemic continued to run its natural course perhaps 70 to 75 per cent of the susceptible children or approximately 7,000 children might have had the disease. As many as 10 per cent of these or about 700 could be expected to have significant sequellae. Aborting the epidemic therefore could spare a large number of children in the county from serious disease.

Several secondary objectives were also substantially achieved by the campaign. It was demonstrated that a community immunization campaign can be planned and organized quickly. It was also shown that the public will respond readily to such a campaign. The Hypospray Jet Injector Guns were shown to be safe and helpful in attempting large-scale immunization campaigns. Of particular gratification to all involved was the cooperative atmosphere and the enthusiasm for the campaign demonstrated by all the personnel involved. People from three government levels and from the community at large worked together as a team in an effort to achieve a major health objective for a community.

WOMAN'S AUXILIARY

to the California Medical Association

Keeping Pace

LIFE HAS always changed. Never in the history of the world, however, has it changed with such rapidity as it does today.

"One thing that is new is the *prevalence of newness,* the changing scale and scope of change itself," observed scientist J. Robert Oppenheimer.

This new pace of change has begun to affect every facet of American life. Current political and social issues have arisen out of the real concern over the swiftness and quality of change. Surely change is at the heart of the medical-political issues of the day. Reactions to this change vary, among Auxiliary members, from cool, uncommitted aloofness, to deep anxiety, to resolute determination to control the direction of the change and preserve enduring values amidst the flux.

A second significant and alarming factor is the atmosphere of *adjustment vs. contribution.* Man today is drawn early into a vocation and "adjusts" to society, rather than making a positive contribution to it. There is a tendency toward conformity and sameness, while creative individuality is frowned upon.

The chief task of education is to shape the man —to guide him toward his own achievement. The formal period of education merely points a finger in the direction one must go; it is merely a beginning of what must be continued throughout life.

Here, Program finds its place. The entire field of human activity—work, friendship, love, art, music and poetry—can exert as powerful an influence on man as the formal process of education. Indeed, the liberally educated man knows how to enrich himself and others. His education opens the door to a vital life in the society of men. A man must be something himself, before he can convey anything of value to others. If we fail to educate our members, they will become scientific drones.

The aim of the Auxiliary Program is twofold:

1. To educate our own members; to train and guide them toward a life of constructive action in the promotion of health, peace, justice and love.
2. To educate the poorly informed and interpret the medical profession's stand on social issues.

It was Ernest Cherrington who said, "We are now at the stage where the main emphasis must be laid on the dissemination of the truth. We need, as we have never needed, a campaign of education, with men and women going hither and thither in a great lecture campaign, weaving it across the nation like a weaver's shuttle."

There is one certainty: We cannot afford to be perplexed and groping, for everything we have honored for years seems to be crumbling. Nor can we return leisurely to the habits of the past. We must keep alive a sense of joy, a knowledge of traditions and values, a respect for the individual against bureaucratic depersonalization.

There is a lot of womanpower within the Medical Auxiliary (California's being the largest Auxiliary in the country), with talent, energy and will that can be utilized for progress.

These women cannot contribute, however, if they do not *know.* Through Program, physicians' wives become well informed and can provide a real extension of organized medicine into their communities. Through Program, physicians' wives are acquainted with the unmet needs of the communities and stimulated to do something about them.

A wide variety of projects—Legislation, Health Careers, AMA-ERF, Community Service, International Health Activities, to name only a few—enable Auxiliary members to demonstrate, through service, the very sincere concern of the medical profession for humanity.

A balance must be struck, however. When too much emphasis is placed upon *projects* and not enough upon *educating members* regarding aims and goals, there occurs a situation similar to sitting in a rocking chair—you achieve a sense of action without really going anywhere. *Know thyself* is the watchword for those who would provide leadership.

There has occurred a "program explosion" as well as a "population explosion." The entire concept of Program has greatly expanded. No longer is Program simply 40 or 50 minutes of planned monthly entertainment—a series of films, speakers or panels. Program includes all we learn and do within Auxiliary. It is our *overall plan, effort, action and accomplishment.*

Inasmuch as Program has no subject matter pertaining to itself alone, the Program Chairman is the coordinator of all of the other Auxiliary committees. Through Program she must create opportunities for each of the other chairmen to present materials that reflect Auxiliary aims and goals. She must provide opportunities for friendship, opportunities for Auxiliary to become a training ground for civic leadership, opportunities to "tell the medical story" to the public. And she must serve as the Auxiliary teacher, constantly orientating and educating members.

Among other things, the Woman's Auxiliary is medicine's diplomatic service. As the prime educational instrument of this diplomacy, Program enables us to fulfill the motto of the Auxiliary's president, Mrs. Samuel Bacon, "MAGNIFY YOUR CALLING, M.D.'S WIFE!"

MRS. KENNETH J. MCNIECE
Second Vice President and
Program Chairman

LETTERS *to the Editor*

Control of Post-transfusion Hepatitis

In a recent review of post-transfusion hepatitis in California Medicine (April 1966) Allen[2] has offered a control measure that is impractical, unworkable, and cause for concern to the committees on blood banks of the California Medical Association and Los Angeles County Medical Association and many other physicians involved in transfusion therapy. Briefly, he states the incidence of post-transfusion hepatitis to be increased 10-fold when donors from prison and skid row blood banks are used. And to lessen this hazard, he suggests that for each transfusion, the physician who has ordered the blood (and his patient!) be apprised of the source of the blood to be used in order that they (including the patient) can assess the added risk of hepatitis in relation to the need for the transfusion. Allen believes that there will be instances when there is valid medical indication for blood from volunteer donors but not from commercial sources. He acknowledges the need for blood from commercial blood banks but recommends its use be limited to urgent situations in which the added risk of hepatitis is offset by the medical need.

The blood bank committees of the California Medical Association and the Los Angeles County Medical Association do not agree with Allen in his basic premise nor do they believe that as a control measure for post-transfusion hepatitis his recommendation is sound. The dangerous donor in regard to hepatitis is the asymptomatic carrier of the virus, *not* the patient who recovers from an attack of jaundice. Allen[1] himself learned this many years ago when he reported that on recall of 412 suspect donors to the University of Chicago Clinics, questioning regarding possible attack of hepatitis was fruitless. Hepatitis cannot be prevented by careful donor history, regardless of the source of the donor. We repeat that the major source of virus in a donor population is the asymptomatic carrier who cannot be detected by donor history.

Allen states that the number of cases resulting from single transfusion when the donors are of the prison-Skid Row variety is 10 times greater than the number of cases resulting when the donors are volunteers, members of family or friends. "These results are striking; however, they have been confirmed by other investigators." Allen has misquoted his references. Mirick[4] reports a *slightly* higher attack rate (not 10 times) in one hospital using blood from commercial sources, when compared with another using Red Cross blood, but states that the difference may be explained by the use of more blood. Mosley's[5] report does not deal with source of blood but rather contrasts attack rates in varying states (New Jersey is 100 times as high as Wisconsin), and relates incidence to various blood fractions and components. Allen's observations are not confirmed by the investigations he cites.

In still another area we believe that Allen is in error. He lumps prison donors with those of commercial banks, and in this he has little data to support his belief. In his study at the University of Chicago Clinics he contrasted volunteer donors with prison inmates. His study did *not* include commercial blood banks. We believe that the evidence for greater hepatitis hazard of blood from prisoners relates to the high incidence of narcotic addiction and not to unreliable donor histories.

Indiscriminate transfer of data from prison donor to commercial blood banks is not justified. Kunin,[3] studying the problem of donor source and its relation to hepatitis in two V.A. hospitals in the Boston area has concluded that blood derived from a single commercial source was responsible for a *small* but a significant higher incidence of hepatitis. In this study three commercial blood banks were included and only one of these differed significantly from the others. When expressed in the other manner, two of the three commercial blood banks did *not* differ from the Red Cross or V.A. donors in regard to the incidence of post-transfusion hepatitis.

The committees on blood banks of the California Medical Association and the Los Angeles County Medical Association recognize serum hepatitis as the most important unsolved problem related to blood transfusion which is not preventable by methods available today. They believe that efforts should be made to reduce this hazard but differ sharply with Allen regarding control measures which may be effective. These recommendations are as follows:

(1) Make maximum effort to recruit volunteers (non-paid) donors by use of predeposit plans, pregnancy clubs, replacement schemes, etc. The medical profession should vigorously support the blood program of its local community blood bank, be it Red Cross or non-Red Cross. The volunteer donor should be the backbone of the transfusion services.

(2) Do not use prison donors.

(3) Utilize commercial blood banks for supplemental supply only. Only those commercial banks should be utilized that have adequate medical supervision and have been licensed by the California Department of Health or the National Institutes of Health.

(4) Restrict the use of blood and its icterogenic fractions to patients presenting valid medical need of transfusion. In each case serious and careful consideration should be given alternate modes of therapy.

(5) Report promptly all patients who develop post-transfusion hepatitis to the source of the blood so that the donor involved may be excluded from future donation except for blood fractions or derivatives not known to be icterogenic.

We believe that a program based on these principles will substantially reduce the hazard of post-transfusion hepatitis.

E. R. Jennings, M.D.
Chairman, Committee on Blood Banks,
California Medical Association

J. J. Palmer, M.D.
Chairman, Committee on Blood Banks,
Los Angeles County Medical Association

BIBLIOGRAPHY

1. Allen, J. G.: The current status of six months room temperature stored liquid plasma drawn from healthy donors, Bull. Am. Assoc. Blood Banks, 8:13-16, 1955.

2. Allen, J. G.: Post-transfusion hepatitis, a serious clinical problem, Calif. Med., 104:293-299, April 1966.

3. Kunin, C. M.: Serum hepatitis from whole blood: Incidence and relation to source of blood, Am. J. of Med. Sc., 237:293-303, 1959.

4. Mirik, G. S., Ward, R., and McCollum, R. W.: Modification of post-transfusion hepatitis by gamma globulin, N.E.J.M., 273:59-65, 1965.

5. Mosley, J. W.: The surveillance of transfusion-associated viral hepatitis, J.A.M.A., 193:1007-1010, 20 September 1965.

The Author Replies

Dr. J. Garrott Allen, *author of the article which engendered the foregoing statement, was given opportunity to review the communication before publication. His comments on it follow.*

I FIND no particular disagreement with most of the above comments by Dr. E. R. Jennings, Chairman, Committee on Blood Banks, California Medical Association, and Dr. J. J. Palmer, Chairman, Committee on Blood Banks, Los Angeles County Medical Association. In reply, perhaps it is well first to see where they concur with the thoughts I expressed in the article alluded to.

First, they concur that the volunteer non-paid donor should be the backbone of the transfusion services.

Second, they feel that the use of the prison donor as a source of blood is a practice that should be abolished; I believe this is highly desirable, if it can be accomplished. I would also urge we discontinue the use of donors from the Skid Row population.

Third, they also believe that careful consideration should be given to the use of nonicterogenic agents before or, if possible, instead of, the use of blood.

Fourth, they also urge that cases of post-transfusion hepatitis be reported promptly to the blood supplier (blood bank or distributor) and to this I would add, to the County Health Departments, which is a requirement of the California State Board of Public Health, but this regulation has not been frequently observed. There is little purpose in reporting such cases to blood banks if they are not also reported to health departments. For example, in 1965 there were 374 cases of hepatitis reported in Santa Clara County, California, of which only three were reported as transfusion-associated; one of these three was a case of mine. While Drs. Jennings and Palmer and I agree on the need for reporting, they do not allude to the fact that the existing methods have thus far proved ineffective and need to be revised and properly enforced.

Fifth, they agree with my statements that it is the occult carrier who poses the real problem and that he is encountered with such increased frequency in the prison (and Skid Row) populations that these populations should not be used as the source of blood for transfusion purposes. Drug addiction and sanitary conditions probably contribute, though additional factors cannot be excluded.

As for my references, none are "misquoted" in my article because none are quoted. I can, however, appreciate the concern of Drs. Jennings and Palmer about them and to an extent they are justified. Perhaps an explanation is indicated. When asked to prepare this article for CALIFORNIA MEDICINE, these were the instructions given: "Again a note about references: Hold them down as much as you can, keeping in mind that probably most of our readers will be interested in your report of what you've gleaned from the literature but that only a few will undertake to read all the background articles." I therefore chose four fairly recent references which discussed broad aspects of this subject and which listed other references so that the reader wishing to do so could easily document my statements. Perhaps I did try to stretch these references too far. I would be pleased to supply additional references upon request.

It therefore appears that the only point upon which Drs. Jennings and Palmer actually take issue with my article is my statement that, since blood containers are not labeled to indicate whether the blood is drawn from a high-risk or low-risk donor population, ". . . it is not possible for the physician to explain to his patient that he must accept a product that could be substandard—that the blood from such sources carries a greater than usual hazard of causing serum hepatitis . . . the physician cannot asume his proper role in prescribing blood —namely, to select, when possible, the safest product for his patient." Presumably this is objected to on the grounds that such a procedure is an admission that there is a difference between the incidence rates of serum hepatitis from the prison-Skid Row populations and those from populations representing the community volunteer donors. Although they appear to acknowledge this difference, since they recommend avoidance of the use of prison blood donors, they apparently believe it to be impractical to label such blood so that the patient's physician can be informed that the only blood available is one that carries a potentially much greater risk because it comes from such donor populations. Actually, to make this known would entail nothing but a different label attached to the container and making an appropriate record, and this certainly seems both practical and feasible. The physician may or may not be influenced thereby but at least he has the choice. Of course, such a procedure will become unnecessary when we are assured that suppliers no longer draw blood from high-risk populations for purposes of transfusions or when some method for effectively ridding infected blood of the hepatitis viruses is made available.

In the National Research Council's "General Principles of Blood Transfusion" (1963) the following statements appear in the section entitled "Legal Considerations," under the subheading of *Homologous Serum Hepatitis:* "However, it must be noted that assumption of risk implies knowledge of the risk or risks involved. It is to be emphasized that the courts have ruled in ever-increasing numbers of cases that consent by a patient to any procedure with known potentially bad results is not a knowledgeable consent unless he is explicitly instructed about the possible bad results."

Finally, it is clear that the five-point recommendations of the committees on blood banks of the California Medical Association and the Los Angeles County Medical Association do not differ in principle from mine except that mine include the recommendation that to obtain better quality-control of blood used for transfusion purposes, state and federal health authorities should enter the picture because blood is shipped between hospitals, between cities, between counties, between states, and between countries. Transfusion hepatitis is a worldwide problem.

Respectfully,

J. GARROTT ALLEN, M.D.

INFORMATION

WMA Declaration of Helsinki Serves as Guide to Physicians

THE TEXT of the Declaration of Helsinki adopted by the 1964 World Medical Association Assembly follows:

Introduction

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics which declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research.

It must be stressed that the standards, as drafted, are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison with foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely-given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

Nontherapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

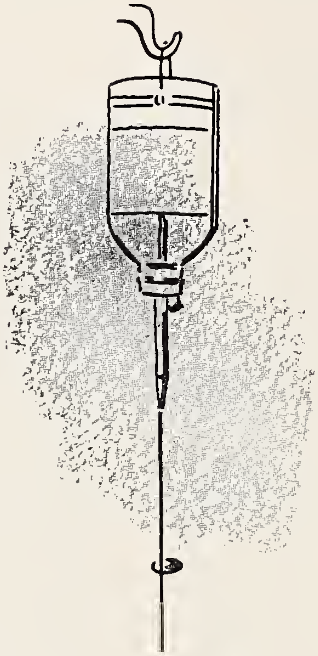
3b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research, the subject or his guardian should be free to withdraw permission for research to be continued.

The investigator or the investigating team should discontinue the research if in his or their judgment, it may, if continued, be harmful to the individual.



NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Dr. John L. Gompertz has been elected president of the **California Thoracic Society**, medical arm of the Tuberculosis and Health Association of California. Dr. Gompertz is a past president of both the Alameda County and the California Tuberculosis and Health Associations. He serves on the Board of Directors of the Family Service Bureau in Oakland. He is a member of the board of directors of the National Tuberculosis Association.

LOS ANGELES

Four physicians on the faculty of the University of Southern California School of Medicine were presented with an **Honors Achievement Award** by the Angiology Research Foundation of New York at a special ceremony recently at Los Angeles County General Hospital.

The award, given in recognition of significant contribution to the literature of vascular medicine and surgery, went to Drs. John L. Johnson, USC associate clinical professor of pediatrics and director of the Cardiac Catheterization Laboratory; George Jacobson, chief radiologist and chairman of the USC Department of Radiology; A. Franklin Turner, USC assistant professor of radiology; and Victor G. Mikity, USC associate professor of radiology. A duplicate award was presented to Los Angeles County Hospital, where the research was carried out, for its role in providing an atmosphere which fosters such efforts.

* * *

Cedars-Sinai Medical Center has announced receipt of a $9,000 grant by the Southern California Chapter of the Arthritis Foundation to provide treatment for medically indigent patients. Grant funds will help provide medical, diagnostic and rehabilitative treatments for medically indigent arthritis patients at outpatient clinics at Mount Sinai and Cedars of Lebanon Hospital Divisions of the medical center.

SAN FRANCISCO

Appointment of **Robert Allen Fishman**, M.D., as professor and chairman of the **Department of Neurology**, University of California School of Medicine, San Francisco, was announced by U.C. President Clark Kerr and Dr. Willard C. Fleming, chancellor of the Medical Center.

His appointment was effective 1 July 1966. He succeeds Dr. Robert B. Aird who was chairman from 1947 to the present. Dr. Fishman was associate professor of neurology at Columbia University.

SANTA CLARA

Stanford School of Medicine physicians searching for new methods of treatment for patients with **acute respiratory problems** have just received a three-year grant of $248,000 to continue their project.

The grant to a team of anesthesiologists headed by Dr. John P. Bunker, professor and head of the Department of Anesthesia, comes from the John A. Hartford Foundation, Inc., of New York. It brings to more than half a million dollars the amount Stanford has received from the foundation for research in the management of acute disturbances in respiration since 1963.

* * *

Dr. Henry S. Kaplan, professor and executive head of the department of radiology at Stanford University School of Medicine, has been elected **president of the American Association for Cancer Research**, a scientific society with more than 1,000 members throughout North and South America. Membership is composed of scientists who have contributed original and significant research in a variety of biomedical fields.

YOLO

Three new staff members have been appointed to the School of Medicine at the University of California, Davis. They are:

Dr. Robert J. Bolt, who will be professor of internal medicine, chairman of the Department of Internal Medicine, and chief of the Division of Medicine. Dr. Bolt has been on the University of Michigan Medical School staff since 1951.

Dr. Loren D. Carlson, to be professor of physiology, chairman of the Department of Physiology, chief of the Division of Sciences basic to medicine, and assistant dean of the medical school. He is at present professor and chairman of the department of physiology and biophysics at the University of Kentucky College of Medicine.

Dr. John Beljan, who will be assistant professor of surgery, is at present medical director of Stuart Drug Co. and a specialist in clinical surgery and aerospace medicine. He was a member of the Department of Defense Task Force for Project Gemini in 1964-65 while hospital commander at Ferrin Air Force Base in Texas.

GENERAL

A prize of $2,500 will be awarded by the University of Colorado School of Medicine to the author of **the best paper on "Thrombophlebitis and Basic Vascular Problems"** in the fifth annual national Cochems Competition. Funds for the prize were provided in the will of the late Mrs. Jane Nugent Cochems of Denver. The competition is open to all persons holding doctorate degrees who are citizens of the United States.

Deadline for manuscripts is 15 November 1966. Inquiries regarding the competition may be addressed to Dr. John J. Conger, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 80220.

* * *

To help in **a survey** to ascertain the social, educational and medical status of **persons with hemophilia**, the Hemophilia Rehabilitation Project at Orthopaedic Hospital, 2400 South Flower Street, Los Angeles, is calling upon physicians in nine Southern California counties to send to the Project the names and addresses of any such patients they may have in their care (including those with Christmas and Von Willebrands disease).

It is proposed that a questionnaire be mailed to the patient by the Project but, if a physician prefers, it will be mailed directly to him so that he may get the information from the patient and relay it to the Project.

The counties to be covered by the survey are: Kern, Los Angeles, Orange, Riverside, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, and Ventura.

The Physician's BOOKSHELF

THE MAYO LEGACY—Gunther W. Nagel, M.D., Emeritus Clinical Professor of Surgery, Stanford University School of Medicine, Palo Alto, California. Charles C Thomas, Publisher, Springfield, Ill., 1966. 157 pages, $6.00.

This short book of 160 pages tells in a very personal way the great story of the development of the Mayo Clinic, the lives and personalities of Dr. William J. and Dr. Charles H. Mayo and of their associates during the 1920's when the author had close, intimate contact with them during a six year period of training in the Clinic, the Mayo Graduate School of Medicine and St. Mary's Hospital in Rochester, Minnesota. In it one will find in a most pleasant and readable fashion, for the layman and for the physician, the often repeated story of the old fashioned, simple virtues and truths which make men great.

In this particular instance the men were physicians and surgeons in a small mid-Western town who arrived on the medical scene at a time when aseptic surgery was at its beginning. The brothers Mayo not only helped to develop knowledge of surgery and what it could accomplish—they were for years among its greatest leaders. Their heritage to mankind was through their contributions to surgery, to graduate and continuing medical education and to the group practice of medicine, all of which were equally outstanding, and constitute the essence of the Mayo legacy.

To see all this through the eyes of an eager young student in surgery learning to become a surgeon is a most pleasant experience for a short evening of reading.

DWIGHT L. WILBUR, M.D.

* * *

PREIMPLANTATION STAGES OF PREGNANCY—Ciba Foundation Symposium—Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F. I. Biol. and Maeve O'Connor, B.A., Little, Brown and Company, Boston, Mass., 1965. 430 pages $13.50.

I feel that this book would be far more aptly titled "Preimplantation Stages of Embryogenesis." The word pregnancy connotes a point of view skewed toward maternal factors and physiology. The emphasis in this volume, however, is very heavily laid on the female gamete from prefertilization stages to the development of the blastocyst, both in vivo and in vitro.

Only in the last few years have these early developmental stages in mammals been the subject of intense and penetrating study on a broad front by scientists who are equipped to bring the most modern concepts and techniques to bear on this area of biological research. It has been said that science grows most rapidly in those areas where separate fields overlap. I can think of no better examples to bear this out than many of the papers presented in this book. Morphology, biochemistry, genetics, molecular biology, mathematics and classical biology are all relevantly and competently used. Mammalian ova, zygotes and blastocysts are very difficult to obtain and they are extremely rare. It is, therefore, no surprise that this field of investigation has developed slowly. That it has by now achieved great vitality and sophistication can be gleaned from this volume based on a Ciba Foundation Symposium held in London, April 1965. Most of the leaders in the field were present and the papers were followed by detailed discussion which has been preserved in the text. One can use the word "indispensable" to describe the book to those who are interested in a comprehensive view of the state of the art in basic investigation of the nature of and the factors controlling preimplantation mammalian development. As is generally true of scientific symposia the clinician will find intellectual stimulation, but little or nothing or practical applicability to medical problems. To convey an impression of the nature of this book, I shall outline a few of the highlights.

Austin presented a study of changes that occur in mammalian eggs during fertilization, as revealed by the electron microscope. Then Enders and Schlafke provided information on the ultrastructure of the blastocysts of several mammalian species. Many species differences were observed but it is intriguing to learn that in the early blastocyst, trophoblast cells differ very little from inner mass cells. Only in late blastocysts does trophoblast cell ultrastructure differ markedly from those cells destined to form the embryo proper.

A number of papers are concerned with the cultivation in vitro of mammalian eggs. Mouse eggs appear particularly amenable to this kind of experimental manipulation. Defined culture conditions have been found that allow development from the two cell stage to the blastocyst. Substrate requirements vary according to the stage at which the eggs are taken from the female genital tract. Such an approach obviously provides vast new opportunities for experimental work on requirements for growth and differentiation and on mechanisms of interference with these processes.

The transplantation of ova from the genital tract to other sites in mice (including transplantation into male hosts) has yielded fascinating information on the inherent capacities of the developing ovum to implant and/or to give rise to embryonic tissue. It appears that exposure to a uterine environment for at least a short time is prerequisite for embryonic tissue development. Lack of this exposure, however, does not prevent growth of extraembryonic tissue from ova transplanted to various sites in a host animal.

The experiments of Mintz and of Tarkowski show that genetic mosaicism can be readily induced in mice at various cleavage stages (two cell stage to late morula). Two or more mouse ova can be deprived of their zona pellucida and the resultant cells will fuse to form one compact mass that can develop into single but giant blastocysts. Some of these blastocysts develop past birth and show evidence that most tissues of their bodies are made up of intermingled cells derived from the two or more ova used to form the single blastocyst. Occasionally true hermaphrodites develop after this kind of manipulation and indicate the possible role of sex chromosome mosaicism in the genesis of this disorder.

LOUIS FRIDHANDLER, M.D.

YOUR ULCER: PREVENTION, CONTROL, CURE—G. S. Serino, M.D., M.Sc. (Surg.), F.I.C.S. Illustrated by Lois Carl Fargo. J. B. Lippincott Company, Philadelphia and New York, 1966. 162 pages, $3.50.

A disease such as a peptic ulcer, which may affect some 10 per cent of the population of the United States, is certain to inspire the writing of a number of books for the general public. Here is one such book, written by a physician who has not only had an ulcer but cured it himself. Dr. Serino hopes that his book will serve practicing physicians as "an up-to-date handbook . . . to place facts, findings and trends at their easy disposal." His principal aim, however, is to bring laymen some basic knowledge on the cause, cure and prevention of ulcer.

Dr. Serino has written this book "with many people in mind: those who now suffer from an ulcer: those who have recovered: and those who have reason to fear the development of one. Those who suffer from an active peptic ulcer must understand the nature of their ailment and try to appreciate the reason why the doctor prescribes a particular treatment. This book aims to provide such essential information; it does not offer miracle cures, but it truthfully presents the facts which can open the way to cure and leave no doubt that a cure is possible."

The reviewer feels that the book can indeed be of help to the person who has a diagnosed ulcer, and recommends it to physicians for such reference. However, he hesitates to recommend it for those who have never had an ulcer—and particularly those who may think or fear that they have one—because of the possibility of self-diagnosis and anxiety of prognosis.

Chapter 17, entitled *Drugs That Help,* is unfortunately a plug, albeit a brief one, for certain brand-name drugs. It would be better if the author had used generic terms and gone into more detailed explanation than he does.

Dr. Serino's prescription for avoiding recurring ulcer is succinct: "You must strive to stay in good shape physically and psychologically." The basic ground rules he advises include rest, emotional equilibrium, avoidance of infection and a common sense approach to diet, smoking, drinking and physical activity. No more can one ask!

EDGAR WAYBURN, M.D.

* * *

SYMPOSIUM ON VASCULAR DISORDERS OF THE EYE—Basic Considerations in Anatomy and Physiology—Sponsored by The Visual Sciences Study Section, Division of Research Grants, N.I.H. (P.H.S. Conference Grant NB 05516-01 from the National Institute of Neurological Diseases and Blindness) and The Department of Ophthalmology, Presbyterian Medical Center, San Francisco. Subcommittee on vascular disorders: Jerome W. Bettman, Chairman; Raymond A. Allen; Calvin Hanna and Marie A. Jakus. Advisers to the committee: Edward W. D. Norton and Kenneth Swan. From articles appearing in the December 1965 issue of Investigative Ophthalmology. The C. V. Mosby Company, St. Louis, Mo., 1966. 186 pages, $12.50.

The papers are presented primarily to stimulate further research in this particular field of ocular disorders. The authors consist of both clinical ophthalmologists and basic scientists in other disciplines of medicine. The clinical ophthalmologist reading this text will not find many pearls to help him in handling these types of diseases.

This symposium is recommended for ophthalmologists interested in this field and as a reference text in hospital and local medical society libraries.

R. M. SINSKEY, M.D.

A DIAGNOSTIC APPROACH TO CHEST DISEASES—Differential Diagnoses Based on Roentgenographic Patterns—Glen A. Lillington, B.Sc., M.D., M.S. (Med.), F.R.C.P. (C), Section of Medicine, Palo Alto Medical Clinic; Research Associate, Palo Alto Medical Research Foundation; Clinical Assistant Professor of Medicine, Stanford University School of Medicine; and Robert W. Jamplis, B.A., M.D., M.S. (Surg.), F.A.C.S., Section of Thoracic Surgery, Palo Alto Medical Clinic; Research Associate, Palo Alto Medical Research Foundation; Clinical Assistant Professor of Surgery, Stanford University School of Medicine. The Williams & Wilkins Company, Baltimore, Md., 1965. 508 pages, $14.50.

This monograph is a unique and highly practical description of the reasoning process commonly employed by experts in the diagnosis of chest diseases. The authors have avoided the usual textbook methods and hence have not included a quantity of useless material commonly associated with textbooks. The reader should first consult the introductory pages which clearly describe the intent of the book and how it may be used most effectively.

After careful study of the volume I can find nothing to criticize and can recommend this without reservation to anyone who is concerned with the diagnosis of thoracic disorders.

Obviously, this book cannot be encyclopedic and many of the rare pulmonary disorders are mentioned briefly, if at all. The authors have succeeded in accomplishing the goal they set very well.

The illustrations are of good quality, the book is easy to read with clearly expressed descriptions and sound logical opinions. It is not intended for radiologists, nor is it intended to replace the radiologist, but it provides for the attending physician an excellent guide through the maze of diagnostic possibilities which are frequently confronting him following the report of an abnormal roentgenogram of the chest.

H. CORWIN HINSHAW, M.D.

* * *

BLOOD DISEASES OF INFANCY AND CHILDHOOD—Second Edition—Carl H. Smith, M.A., M.D., Clinical Professor of Pediatrics, Cornell University Medical College, New York, N.Y.; Consulting Pediatrician, The New York Hospital, New York, N.Y.; Beekman-Downtown Hospital, New York, N.Y. The C. V. Mosby Company, St. Louis, Mo., 1966. 800 pages, $22.00.

Carl Smith's "Blood Diseases of Infancy and Childhood" is probably *the* classic textbook on the subject of Pediatric Hematology. This book belongs in the library of all hospitals or medical centers caring for pediatric patients. It is generally a practical book concerning itself chiefly with diagnosis and therapy of pediatric hematological problems. Because of the very basic as well as clinical nature of this book it might be well considered for the library of any practicing pediatrician, general practitioner, medical student, pediatric house staff or laboratory technologist.

The chapters are well organized and the information succinctly presented. There is a very detailed bibliography, which enables the reader to obtain further information or details if desired. Current references are listed at the end of each of the chapters, totaling over 1,500.

This second edition brings up to date hematological advances and changes since the first edition was published in 1960. Improvements or changes since the first edition include among others the chapter on jaundice which presents, in considerable detail, the current controversy regarding management of neonatal hyperbilirubinemia. Management differs when it is due to different causes such as prematurity or breast milk conjugation inhibition. The chapter on hemoglobinopathies adds current data on the new abnormal hemoglobins. The treatment of leukemia has had several new useful agents added to the armamentarium. New methods of administration, relating to dose schedule and routes of administration of some of the standard agents are currently being revised, often with beneficial results. The very useful technique of amniocentesis is thoroughly reviewed as a valuable adjunct in the prediction of the severity of hemolytic disease of the newborn. Intrauterine transfusions to save severely hydropic and phehydropic erythroblastotic babies is discussed. Coagulation advances are clarified, stress the use of the PTT (Partial thromboplastin time) as one of the best tools in the screening for bleeding problems.

For a basic, thorough, sound and practical book on diagnosis and treatment of Pediatric Hematological Problems, this book is highly recommended.

JOSEPH H. KUSHNER, M.D.

* * *

PSYCHOPATHOLOGY OF PERCEPTION—Edited by Paul H. Hoch, M.D., Department of Mental Hygiene, State of New York; College of Physicians and Surgeons, Columbia University, New York City; and Joseph Zubin, Ph.D., Department of Mental Hygiene, State of New York; Department of Psychology, Columbia University, New York City. (The Proceedings of the Fifty-Third Annual Meeting of the American Psychopathological Association, held in New York City, February 1963). Grune & Stratton, Inc., New York, N.Y., 1965. 336 pages, $12.50.

This volume comprises 13 papers delivered at the 53rd Annual Meeting of the American Psychopathological Association in New York City, February 1963. While each of the papers attempted to concern itself with the theme of the meeting, namely, the psychopathology of perception, the general reader may find himself somewhat confused by difficult semantics concerning the term "perception." The difficulties ensue from an attempt to fit topics as varied as the organization of motor activity and psychological defense under the rubric of perception. The semantic difficulties can be anticipated by brief consideration of the broad usage allowed for the term "perception" and the adjective "perceptual." For example, in the preface to this volume the editors allow that the three elements that are involved in any "perceptual task" include "sensory afferents, reticular activating systems, and cortical association activity" or "sensory input, alertness or arousal, and memory storage." Dement, in his paper on perception during sleep broadens the definition even more by allowing that perception can be defined as that which intervenes between sensory stimulation and awareness, or that which intervenes between sensory stimulation and behavior. While many of the individual authors struggle to fit their work into a perceptual frame of reference or to broaden perception to include their work, this in no way detracts from the many excellent papers which contain discoveries of fact as well as stimulating theoretical innovations. However, the potential reader should be forewarned that his own "perceptual set" conditioned by the title of the volume may cause difficulties in his approach to some of the valuable material therein.

The book is divided into three general parts; the first dealing with the neuro-physiology of perception, the second with the psychopathology of pain, taste and time, and the third with perception under special conditions, particularly those of sensory deprivation, emotional loading, and sleep. Included in the first part, the neurophysiology of perception, is a very intriguing paper by Dr. Heinrich Klüver. Dr. Klüver's paper on the neuro-biology of normal and abnormal perception was presented to the American Psychopathological Association as the 1963 Samuel H. Hamilton award lecture. Dr. Klüver was introduced by Dr. Paul C. Bucy, and the reader will find in Dr. Bucy's introduction and Dr. Klüver's paper a stimulating review and re-analysis of the Klüver-Bucy Syndrome (temporal lobe syndrome) which bears their names. Dr. Klüver's paper has a wide reaching scope as he moves from a discussion of hallucinations and porphyria into a review of the temporal lobe syndrome and then more generally into limbic system functioning. He makes a stimulating analysis of the similarities between olfaction, emotion, and sex-related behavior—the three functions of the limbic system—and then relates the common characteristics of these functions to the characteristics of hallucinations. He concludes that the temporal lobe syndrome implies a "de-differentiation of functions" and that the instability, fluctuations, and oscillations characteristic of olfactory, emotional, and sexual phenomena are also characteristic of hallucinatory phenomena. These phenomena are examples of functions involving fluctuations and inconsistencies and such functions are, Dr. Klüver suggests, the functions of the temporal lobes and especially the temporal rhinecephalon.

The second paper dealing with the neurophysiology of perception is one of Dr. Charles Shagass' many contributions to the study of cortical evoked potentials in psychopathology. Dr. Shagass finds differences in both amplitude and recovery time of cortical evoked responses when he compares certain clinical groups with each other. Disquieting is the finding that while his results differentiate a normal population from many psychiatric entities, they do not differentiate the schizophrenias or function psychoses from the group defined as "personality disorders." One wishes that as much detail were presented concerning the selection of the clinical population as is presented concerning the complex methodology involved in studying somatosensory and visual evoked potentials. The third paper in the first part of the volume, by Dr. Gregory Razran, is an interesting review of Russian experimental work on interoceptive stimulation. The implication that not only can anxiety condition the occurrence of, for example, constipation but that sensations of constipation and other bodily sensations can condition the occurrence of anxiety or of other somatic states, will be of interest to those dealing with psychosomatic and related conditions. The final paper in this group by Dr. Richard Allen Chase deals behavioristically with the effects of sensory events on motor tasks.

In the second part, the psychopathology of pain, taste, and time, the paper by Dr. Henry K. Beecher will be of most general use and interest and summarizes the evidence differentiating the "original sensation" of and the "reaction component" to pain. Dr. Beecher demonstrates quite effectively how varied somatic, cultural, situational and psychological influences can modify the reaction component and suggests convincingly that narcotics such as morphine act, primarily, on the reaction component rather than on the original sensation of pain. The paper on the perception of taste by Fischer, Griffin, and Pasamanick deals with the physiochemistry of taste and presents as an additional tidbit some evidence that there may be a genetic predisposition underlying relative nontasters and tasters. The authors have found an associations of high taste thresholds in the parents of mongoloid children. The final paper in this section, the psychopathology of time judgment by Lhamon, Goldstone and Goldfarb demonstrates that schizophrenic patients and normal subjects differ in their estimation of short time intervals. The high emphasis on methodological details of this paper limits interest to those who have a special research interest in this area.

In the final section, Dr. Nolan D. C. Lewis gives an excellent clinical description of the depersonalization syndrome. Two papers deal with environmental deprivation, the first by Theodore Schaefer, Jr., and Niles Bernick gives a critique of the long literature on sensory deprivation and concludes that suggestion and expectation may be the most important factors in eliciting the subjective experience reported as the sensory deprivation syndrome. Dr. Ronald Melzack discusses the effect of restricting the environment of young puppies on later behavior. This paper, as well as the paper on "perceptual defense" by Charles Eriksen, a paper dealing with differential recognition of neutral and emotionally loaded words, both describe their results under the rubric of perceptual change. While such findings as those of Melzack that dogs raised in restricted environments have a difficulty in inhibiting irrelevant responses and do not respond appropriately to sexual stimulation are significant findings, they do not seem necessarily related to perception per se. Dr. Dement's paper on perception during sleep presents another excellent review of the experimental literature on the physiological state of dreaming (referred to as paradoxical sleep, dreaming sleep or REMS sleep) and differentiates hypnagogic states from dreaming in terms of the lack of significant autonomic and other physiological changes accompanying the former as compared with the latter.

The index to this volume is scanty relative to the wealth of data presented. This, the form of presentation of most of the papers, and the nature of the topics discussed will make this book of most interest to the specialist and researcher who is already acquainted with the literature in this area.

EDWARD M. ORNITZ, M.D.

* * *

AN OUTLINE OF RADIOGRAPHIC FINDINGS IN MULTIPLE-SYSTEM DISEASE—John H. Simonton, M.D., Assistant Professor of Radiology (in residence), University of California at Los Angeles and Assistant Chief Radiologist, Department of Radiology, Los Angeles County Harbor General Hospital, Torrance, California; and Robert C. Jamison, M.D., Assistant Professor of Radiology (in residence), University of California at Los Angeles and Radiologist in Charge of Diagnosis, Department of Radiology, Los Angeles County Harbor General Hospital, Torrance, Calif. Charles C Thomas, Publisher, Springfield, Ill., 1965. 261 pages, $11.75.

The clinical and radiologic findings in generalized systemic diseases often presents, to the student and practicing physician alike, a bewildering array of abnormalities, difficult to organize into any easy to remember pattern.

This small book presents an amazing quantity of information of more than 90 systemic diseases, with an extensive list of radiological findings for each disease, preceded by a brief description of the clinical findings. Each disease is a separate article, presented in alphabetical order, using the most common name of the disease. Where there are several common names, cross reference is usually provided. The articles include pertinent background information including incidence, etiology, clinical findings, complications and differential diagnosis. Statistics are presented when available, such as age and sex incidence, and the relative frequency of specific clinical and radiological abnormalities. The x-ray findings are usually presented by systems (skeletal, G.I., G.U., etc.). Separate "orientation" articles discuss groups of diseases such as connective tissue diseases, metabolic bone disease, histeocytosis, etc. A short list of select current references are found at the end of each article.

A list of radiological findings are quite complete and accurate and up to date. The clinical information is brief and to the point. Some criticism may be levelled at the non-uniform presentation, for example similar type information is presented under a variety of sub-headings such as "Background," "keynote," "clinical findings," "clinical notes," "definition," "clinical background," "clinical setting," "clinical features," etc. Also, it might have proven slightly more useful if more disease synonyms were listed for cross reference, particularly for the students who may not be aware of all the names of some of these systemic diseases. There are no illustrations and some readers may feel a few selected illustrations would have added value to the book. These criticisms, however, are minor relative to the overall value of the book, which fills a definite need. Radiologists in particular will find it very useful, if not an indispensable volume, but it will also prove valuable to other specialists, residents, and medical students.

WARREN M. RUSSELL, M.D.

* * *

ANIMAL BEHAVIOUR AND DRUG ACTION—Ciba Foundation Symposium (jointly with the Co-ordinating Committee for Symposia on Drug Action). Editors for the Ciba Foundation, A. V. S. De Reuck, M.Sc., D.I.C., and Julie Knight, B.A. Editor for the Co-ordinating Committee, Hannah Steinberg, Ph.D. Little, Brown and Company, Boston, Mass., 1964. 491 pages, $13.00.

This is a report on a Ciba Foundation Symposium in London in March 1963, on the general subject of psychopharmacology of animals. It is composed of three divisions. The first division is a series of formal papers given in four sessions under the headings Behavioural Analysis of Drug Action, Neurophysiological and Biochemical Correlates of Behavioural Effects of Drugs, Factors which Modify Effects of Drugs on Behaviour and Relevance of Behavioural Effects of Drugs in Animals to Effects in Man.

The second division is a transcription of informal discussions entitled Intermediation between Administered Drugs and Behavioural Effects and is composed of four sessions entitled The Biochemical Approach, The Electrophysiological Approach, The Neurophysiological Approach and The Pharmacological Approach. The last division is also made up of transcribed reports of informal discussions on the general subject of The Relevance of Behavioural Effects of Drugs in Animals to their Effects in Man, and this division consists of two sessions entitled Extrapolation from Animals to Man and Clinical Implications. At each of the 10 sessions from three to five reports were presented by individuals or groups actively at work in the fields of neurophysiology, neurochemistry, neuropharmacology and psychopharmacology in both Great Britain and America. The sessions were presided over by such well known British medical biologists as Sir John H. Gaddum, W. S. Feldberg, A. Summerfield, Sir Aubrey Lewis, J. M. Barnes and M. Shepherd.

The role of memory in behavior is emphasized and efforts are made at a scientific description of memory. The language of the book, although technical, is easily understood by those of us who may not have experience in the field in which the author works. Apparently, each paper was aimed at a general, rather than a technically restricted audience. It is of special interest to experimental and clinical pharmacologists and neurologists, psychologists and psychiatrists, but may be read with profit by any one concerned with natural phenomena.

CLINTON H. THIENES, M.D.

OPERATIVE OBSTETRICS—Second Edition—R. Gordon Douglas, Emeritus Professor of Obstetrics and Gynecology, Cornell University Medical College; Consultant in Obstetrics and Gynecology to The New York Hospital and to The Roosevelt Hospital; and William B. Stromme, Clinical Assistant Professor in Obstetrics and Gynecology, University of Minnesota Medical School; Attending Obstetrician and Gynecologist, Northwestern Hospital and Fairview Hospital, Minneapolis. With assistance from Masao Nakamoto, M.D., Chief of Obstetrics, The White Memorial Medical Center; Attending Obstetrician and Gynecologist, The White Memorial Hospital, Los Angeles. Foreword by Nicholson J. Eastman. Appleton-Century-Crofts (Division of Meredith Publishing Company), New York, 1965. 779 pages, $22.50.

This is not merely an atlas of obstetric surgery, as might be inferred from its brief title, but a profusely illustrated textbook concerned with every facet of operative obstetrics and the care of women who require obstetric operations, or operations while pregnant. Prior to its first edition, it was conceived as a companion to *Williams Obstetrics,* the popular general textbook published by the same firm that has turned out the two editions of this operative text. Thus it presents not only the details of how best to accomplish all the usual and even unusual obstetric maneuvers, but it covers such related topics as pelvic anatomy, preoperative care, anesthesia, infant resuscitation, postoperative care, and postoperative complications. There is even a chapter on surgical problems outside the generative tract, particularly those that may be anticipated in any large group of pregnant women, such as appendectomy, cholecystectomy, colostomy, herniorraphy, urinary tract operations and so forth.

The new edition includes virtually all the innovations and new concepts in obstetric practice that have gained appreciable popularity in the last decade, such as external cardiac massage, new anesthetic agents, paracervical block anesthesia, hypertonic saline to effect abortion, the vacuum extractor, and intrauterine transfusion, just to mention a handful. Descriptions and illustrations of several outmoded procedures have been deleted, but 169 new and original illustrations have been added, so that the new edition is a bit thicker than the first.

As the authors suggest in the preface, this book may have particular value for the busy resident who has not had time to learn about alternative techniques while applying the standard procedures of his own institution. Perhaps in the first year or two of private practice, when time for browsing is at hand, he would find it profitable to learn more of the background of those maneuvers with which he already has a certain familiarity, and to discover a number of worthwhile procedures that passed him by in the daily rush of hospital duties and domestic crises. Though this clearly is a volume that should be available in every teaching hospital, I suspect its profusion of detail will not endear it to the average undergraduate medical student, who already staggers under the load of reading the standard textbooks.

Some of the illustrations are borrowed from books and periodicals, but the majority of them are outstandingly good originals. In many instances, photographs of actual situations are supplemented by superb, adjacently placed line drawings showing precisely what was in progress. A fairly extensive list of references concludes each chapter. Certainly this book fills a need in obstetric teaching at the graduate level and can be highly recommended for that purpose. The fact that my personal copy of the earlier edition of Operative Obstetrics has long since permanently disappeared from my office bookshelf perhaps testifies to the popularity of this volume, in Palo Alto at least.

CHARLES E. MCLENNAN, M.D.

FUNDAMENTALS OF CLINICAL HEMATOLOGY—Second Edition—Byrd S. Leavell, M.D., Professor of Internal Medicine; Physician-in-Charge, Hematology Section, School of Medicine, University of Virginia; Attending Physician, University of Virginia Hospital; and Oscar A. Thorup, Jr., M.D., Associate Professor of Internal Medicine; Physician-in-Charge, Hematology Clinic, School of Medicine, University of Virginia; Attending Physician, University of Virginia Hospital. W. B. Saunders Company, Philadelphia, 1966. 597 pages, $12.50.

This is an excellent text which covers the field of hematology. It is well written, easy to read, and has a complete bibliography. Because of its small size it must be quite brief in some areas. The sections include an initial review of the basic scientific aspects of a disease or defect followed by a discussion of the entity associated with the defect. For example, in a presentation of the disorders of vitamin B-12 and folic acid metabolism, there is initial discussion of the mechanisms of action of these vitamins which is followed by a description of clinical disorders characterized by these deficiencies. In each chapter there are divisions related to clinical and laboratory findings as well as brief paragraphs concerning therapy and prognosis. And in many instances pertinent brief case histories are presented.

The chapter entitled "Hemostasis, Theory and Applications" is a noteworthy review of the current status of the factors governing blood clotting. It presents a clear and concise picture of this complicated field.

The charts and tables are simple and pertinent and enhance the written text. However, the book has a minimum of illustrations and perhaps this detracts from some of its presentations. Specifically, in the first chapter where pictures of erythroid and myeloid precursors in the bone marrow included in the paragraphs describing them would have been very helpful. The section on lymphomas could have been improved by the use of descriptions as well as illustrations of the specific histologic alterations of these diseases.

The final section on laboratory procedures with accompanying bibliography is an appropriate addition to a hematologic text.

To summarize, this is an accurate and inclusive text of hematology. It would be most useful for the medical student, and of special interest to the practicing physician who would like to have at his fingertips an available source of concisely written and current information in this field.

ESTHER F. HAYS, M.D.

* * *

MEDICAL DEPARTMENT, UNITED STATES ARMY, SURGERY IN WORLD WAR II—Thoracic Surgery, Volume II—Prepared and published under the direction of Lieutenant General Leonard D. Heaton, The Surgeon General, United States Army. Colonel Arnold Lorentz Ahnfeldt, MC, USA, Editor in Chief; Frank B. Berry, M.D., Editor for Thoracic Surgery; Elizabeth M. McFetridge, M.A., Associate Editor. Office of The Surgeon General, Department of the Army, Washington, D.C., 1965. 615 pages, available for purchase at $7.25 per copy from the Superintendent of Documents, Government Printing Office, Washington, D.C., 20402.

This volume, comprising a part of the official history of the Medical Department of the U.S. Army in World War II, is a carefully edited and interesting account of the management of chest injuries incurred under battlefield conditions during those war years. It is a surprisingly informative and pertinent document, laying down rules of therapy formulated on a wealth of experience which still make up much of the basis of current treatment.

The first volume of this two-volume series, published in 1963, dealt primarily with statistical and administrative material. The present book is divided into three sections: (1) specific types of wounds; (2) complications; and (3) zone of the interior. It contains the meat of what was learned and, in no small sense, represents a milestone in the history of thoracic surgery. The "wet lung" syndrome, for example, is a concept which derived from this era. Its management, including the use of positive pressure ventilation and frequent use of endotracheal suction to maintain a clear airway, has become standard practice during the intervening 20 years. Treatment of hemothorax and contused lung are presented in lucid fashion. The relatively conservative approach presented (repeated thoracenteses or chest tube drainage; avoidance of thoracotomy when possible) is contrasted by the advocacy of an aggressive attack on hemothoracic empyema with formation of a pleural peel. In the latter condition, the authors recommend early pulmonary decortication rather than protracted drainage of the infected pleural space. Delayed resolution of uninfected hemothorax, they feel, should also be treated in similar manner. The low operative mortality reported—less than 2 per cent—resulting from approximately 1,500 decortication procedures stands as a tribute to the excellence of skill and judgment displayed. Although this preference for primary early decortication without drainage over secondary, post-drainage decortication is at variance with current teaching at some centers there is much to be said for it in terms of reduced morbidity and ultimate restoration of normal pulmonary function.

A glance at the pictures on pages 302-3 contrasting the appearance of post-operative cases during World War I with those of World War II brings forth realization of the tremendous improvement in care which developed during that relatively short time span. And, although statistics are de-emphasized in favor of principles, the few which are included are noteworthy. In one hospital during a 10-month period 134 operations for the removal of missiles retained in and about the heart and great vessels were formed without a single fatality. This is indeed an impressive record. The sad experience with combined chest and spinal cord injuries is, by comparison, what might be anticipated.

The illustrations and case reports are numerous and excellent. There are relatively few flaws, although some needless repetition creeps in now and then. The concept of *pendaluft* or pendular breathing following open wounds of the chest is still supported despite recent investigations to the contrary. These are, however, minor criticisms. The final chapter details an attempt to gain long-term follow-up information on more than 150 cases personally treated by one of the authors. It is a masterful and most worthy endeavor. In short, despite the book's title, which suggests a work of rather limited scope and usefulness, this volume is still timely, informative, and historically significant. The authors accomplished their purpose well.

PETER G. GAAL, M.D.

* * *

DIAGNOSIS AND THERAPY OF THE GLAUCOMAS—Second Edition—Bernard Becker, M.D., Professor and Head of the Department of Ophthalmology, Washington University School of Medicine, St. Louis, Mo.; and Robert N. Shaffer, M.D., F.A.C.S., Clinical Professor of Ophthalmology, University of California School of Medicine, San Francisco, Calif. The C. V. Mosby Company, St. Louis, Mo., 1965. 443 pages, $18.50.

This second edition by Becker and Shaffer brings the entire field of glaucoma up to date in a most comprehensive and readable fashion. The text is divided into eight sections which include: 1. Classification; 2. Gonioscopy; 3. Tonometry and tonography; 4. Ophthalmoscopy and perimetry; 5. Diagnosis and therapy; 6. Medical techniques; 7. Surgical techniques, and finally, 8. Appendix.

This edition includes such recent techniques as cyclocryosurgery which is just beginning to break into the glaucoma field. The illustrations are excellent.

I recommend this book very highly for the practitioner of ophthalmology whether he be in a university surrounding or in a relatively isolated town.

R. M. SINSKEY, M.D.

* * *

WILLIAMS OBSTETRICS—Thirteenth Edition—Nicholson J. Eastman, Professor Emeritus of Obstetrics, School of Medicine, The Johns Hopkins University; Obstetrician-in-Chief Emeritus to The Johns Hopkins Hospital, Baltimore, Maryland; and Louis M. Hellman, Professor and Chairman, Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center; Director of Obstetrics and Gynecology, Kings County Hospital, Brooklyn, New York. With the collaboration of Jack A. Pritchard, Professor and Chairman, Department of Obstetrics and Gynecology, Southwestern Medical School; Chief of Obstetrics and Gynecology, Parkland Memorial Hospital, Dallas, Texas; and with the assistance of Ralph M. Wynn, Assistant Professor, Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center. Appleton-Century-Crofts (Division of Meredith Publishing Company), 34 West 33rd Street, New York, N.Y., 1966. 1182 pages, $18.75.

Anyone familiar with recent editions of this widely used textbook will have no trouble recognizing the current version. Only the most minor changes are noted in chapter headings and general format, though a number of new and bolder type faces have been used to good advantage for section headings and for some of the subheadings within chapters. Jack A. Pritchard, chief of obstetrics at Southwestern Medical School, collaborated in the preparation of this edition, and the assistance of Ralph Wynn is attested by the rather liberal use of electron micrographs. A new chapter on the psychosomatic aspects of obstetrics, by Sprague Gardiner of Indianapolis, has replaced Leo Kanner's material on psychiatry in relation to childbirth.

As would be anticipated, the major rewriting was done in the section on the physiology of reproduction, particularly those portions concerning the placenta, as well as fetal physiology and endocrinology. Much new information has been added in the pages describing abortion, disease of the trophoblast, congenital malformations, anesthesia, contraception, and genetic counseling, and numerous minor revisions appear in the chapter on coincidental complications of pregnancy. All this has been accomplished in 57 fewer pages of the text than were used in the previous edition, a notable feat of good editing and good writing.

The bibliographies, always an attractive feature of this textbook, have been pruned and updated to represent an invaluable combination of older classic references and the best available current data and opinions. The index, I am happy to report, is appreciably longer and far more satisfactory to use than its frustrating predecessor in the twelfth edition.

There would seem to be little doubt that *Williams Obstetrics*, despite formidable competition, will retain its well deserved reputation as the most authoritative presentation of American obstetric practice and modern investigative work. Suffice it to say that this book is still a superb effort in every respect. Those who have known it in the past will be pleased by the obvious improvements in the 1966 volume. Those now needing an obstetric text for the first time are urged to look carefully at "the Williams" before investing elsewhere.

C. E. MCLENNAN

HALLUX VALGUS, ALLIED DEFORMITIES OF THE FOREFOOT AND METATARSALGIA—H. Kelikian, M.D., Associate Professor, Department of Orthopaedic Surgery, Northwestern University Medical School and Senior Attending Staff of Chicago Wesley Memorial Hospital. W. B. Saunders Company, Philadelphia, 1965. 503 pages, $19.50.

This reviewer appreciates the labor and toil the author exerted in the preparation of this monograph.

The criticism in this review in no way diminishes the respect for an author who writes a medical book. Only one who has written even an article for a medical journal is aware of the "sweat" that goes into writing scientific medical literature.

This text is a welcome addition to the literature on forefoot diseases. It is an exhaustive compilation of everything that has been written on these deformities from Camper (1791) to the present day; the bulk of this volume is an abstraction of this literature. It is limited to static deformities of the forefoot and their secondary changes. The major part of the book (280 pages) is devoted to the deformities of the first metatarsal phalangeal joint, with only glossary mention of the extrinsic diseases which may contribute to such deformities.

The most valuable contribution the author makes is clarification of the enigmatic and confusing terminology universally applied to these problems. He points out that most first metatarsal phalangeal joint deformities are generally grouped under the heading "bunion" and its unscientific derivative "bunionectomy" are used too loosely and indiscriminately. Also, that the term "exostosis," to denote the medical condyle of the first metatarsal head, and its corollary "exostectomy" is generally a misnomer.

The most common deformity grouped under "bunion" is hallux valgus, which as Kelikian points out is a "symptom complex" and finds that "most surgical procedures on record have scant, extremely tenuous and often untenable principles to support them" and that he has merely attempted to "organize the confusion."

The volume is profusely illustrated with line drawings and excellent photographs. Many of the drawings are of procedures described by previous authors. Others are alongside photographs of operations performed by him, or rough graphs of pathological anatomy.

The text is practically an encyclopedia of everything that has been said or written by others about acquired forefoot deformities; however, one has to wade through page after page of this material to find even a modicum of what is rational treatment of these deformities.

This volume may be of value to the student of the history and errors of past judgment of the treatment of deformities of the forefoot, but only of modest help to the practitioner who seeks concise scientific advice on the treatment of these problems. Nevertheless, it is a valuable addition to any physician's library whose interest is in the forefoot diseases.

* * *

CARDIAC EVALUATION IN NORMAL INFANTS—The Clinical and Clinical Laboratory Differentiation Between Normal and Abnormal—Robert F. Ziegler, M.D., Physician-in-Charge, Division of Pediatric Cardiology, Henry Ford Hospital, Detroit, Michigan. The C. V. Mosby Company, St. Louis, 1965. 170 pages, $12.75.

Before one can make the definitive diagnosis of a specific congenital heart defect, it is first necessary to determine whether or not any abnormality exists at all. In the newborn period and early infancy, this diagnostic distinction is frequently quite difficult. Dr. Ziegler's book fills a real need for the non-specialist in pediatric cardiology in this respect.

There is no new and original information in the book. Rather, it is a synthesis of appropriate physiological studies which have appeared in the literature, presented in a form most useful to the clinician who is faced with the problem of evaluating the cardiac status of an infant.

The contents of the book are arranged in the order of the most frequent presenting signs: the problem and evaluation of murmurs, cyanosis, cardiac enlargement and arrhythmias, with sections for the special problems such as recognition of heart failure and cardiac status in respiratory distress, and for the evaluation of the heart in primarily non-cardiac conditions of infancy. He concludes with a bibliography which, although not encyclopedic, should fill the needs of any physician faced with an immediate problem infant.

Ann Sproul, M.D.

* * *

ORAL ANTIDIABETIC THERAPY 1956-1965: WITH PARTICULAR REFERENCE TO TOLBUTAMIDE (ORINASE)—H. A. Tucker, M.D., Medical Division, The Upjohn Company, Kalamazoo, Michigan. Charles C Thomas, Publisher, Springfield, Ill., 1965. 676 pages, $13.50.

This volume, compiled by H. A. Tucker, M.D., who is with the medical division of the Upjohn Co., purports to cover the literature on oral antidiabetic therapy, 1956-1965. The book includes 1,700 references from the medical literature. A chapter is devoted to the literature published during each year since 1956. The literature cited is quite variable and includes publications in well known and scientific journals both here and abroad, and work in less well known local medical journals and occasionally obscure foreign sources. The references themselves, unfortunately, are arranged alphabetically depending upon the first author. There is both an author and subject index. It would be difficult with this type of book organization to gather pertinent references involving a specific subject such as the incidence and severity of drug-induced hypoglycemia with these agents. The author's description and interpretation of the cited literature is quite variable. The descriptions of certain papers are detailed, presumably due to the abstractors' interest in the work, while other references are dealt with in blocks which often include six to nine references.

The binding and printing of this book, as is true for other Charles C Thomas publications, is quite good. This reviewer's major objection to the work is the obvious unbalanced citing of work on tolbutamide (Orinase). Except for literature evaluating or studying a number of oral antidiabetic agents including tolbutamide, this book contains essentially no primary references to chlorpropamide (Diabinase), phenformin (DBI) or the other drugs being studied in this area. In fact, the subject index includes only one reference to chlorpropamide and no references to phenformin.

There is a summary at the end of the text which describes the chemistry, mode of action, accepted uses, and pharmacological preparations of tolbutamide available. The trade name is freely used. No summary is included for the other widely used oral antidiabetic agents.

Thus this reviewer feels that this volume might be more properly titled "Literature on Tolbutamide Therapy, 1956-1965." The need for this book is by those involved in the use and evaluation of this drug. It is not clear how much service is provided by a volume which deals with the published experience of one drug in diabetes therapy as contrasted to the production of a text citing the literature which would deal with general subjects and topics of diabetic treatment in a more integrated fashion.

Richard Horton, M.D.

California Blue Shield Reports XIX Experience

More than two million claims have been processed by California Blue Shield during the first 10 weeks it has administered the California Medical Assistance Program, this state's Title XIX legislation, according to the National Association of Blue Shield Plans.

California Physician's Service-Blue Shield handles administration of professional and drug claims for the California Medical Assistance Program, while the two California Blue Cross organizations process hospital and institutional claims.

About 30 per cent of the claims handled by CPS-Blue Shield since the program was launched March 1 related to physicians' services, while the remainder covered drug, dental and other professional services.

In view of normal claims lag in a new program, the volume experienced thus far probably does not indicate the normal claims flow which may be expected in the future, according to a Plan spokesman. The spokesman also said that it appears claims volume will exceed a million claims monthly.

The California Medical Assistance Program already applies to some one million persons entitled to assistance from the state, and is expected to encompass another half-million or more persons when fully operative. State officials estimate annual costs will be approximately $570 million.

Beneficiaries of the plan are provided a broad spectrum of benefits under the California program. In addition to hospital and medical care, the program provides benefits for dental care, outpatient drugs, nursing home benefits and a broad array of ancillary services.

As of July 1, the state "bought-into" Part B of Medicare for its aged beneficiaries, integrating the state plan with benefits of the federal Medicare program.

The California program incorporates criteria relative to "reasonable charges" and "reasonable costs" that are virtually identical to those of Medicare—Title XVIII.

Administration of CMAP is providing experience which will be used later this year when the California Blue Shield and Blue Cross organizations begin administration of the Federal Medicare program, the Plan reports.

Approximately 300 new employees have been hired and trained by California Blue Shield since the task of fiscal administration was assigned to CPS.

John W. Castellucci, executive vice president of the National Association of Blue Shield Plans, said, "The fact that Blue Shield will now serve 60 per cent of the aged under Medicare is ample proof of Blue Shield's leadership in the medical care prepayment field."

Little – known moments in history No. 1:

Mr. Ra, a sculptor, was commissioned by Queen Nefertiti to do a statue of herself, and by King Tut to do a large lion for his front lawn. Confused by vertigo, Mr. Ra got the whole thing mixed up. Did he get a royal bawling-out!

Antivert® tablets · syrup stops vertigo

(meclizine HCl, nicotinic acid)

Tablets: (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.)
Syrup: (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.)

Most widely prescribed anti-vertigo agent[1]
Complete to moderate relief in 9 out of 10 patients[2]

Antivert, the leading anti-vertigo product,[1] combines meclizine HCl, an outstanding drug for treatment of vestibular dysfunction, with nicotinic acid, a drug of choice for prompt vasodilation. Prescribe Antivert for your patients with vertigo, Meniere's syndrome or allied disorders.

Precautions and contraindications: Frequent, short-lived reactions include: cutaneous flushing, sensations of warmth, tingling and itching, burning of skin, increased gastrointestinal motility, and sebaceous gland activity. In explaining these reactions to the patient, it is suggested that they be regarded as a desirable physiological sign that the nicotinic acid is carrying out its intended function of vasodilation. Because of this vasodilation, severe hypotension and hemorrhage are obvious contraindications to Antivert therapy. Although the incidence of drowsiness and other atropine-like side effects such as dry mouth and blurring of vision is low, the physician should alert the patient to the need for due precautions when engaging in activities where alertness is mandatory. **Use in pregnancy:** A review of available animal data reveals that meclizine exerts a teratogenic response in the rat. While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human fetus. Consequently, consideration should be given to initial use of a nonphenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum.

Dosage: One tablet or one to two teaspoonfuls (5-10 cc.) t.i.d. just before meals. Specific requirements for individual patients should be determined by the physician.

Supplied: Tablets in bottles of 100 and 500. Syrup in pint bottles. Rx only.

References: 1. Based on 1965 data from independent physicians' market survey organization. 2. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

J. B. Roerig and Company
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®
New York, N. Y. 10017

plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.

Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

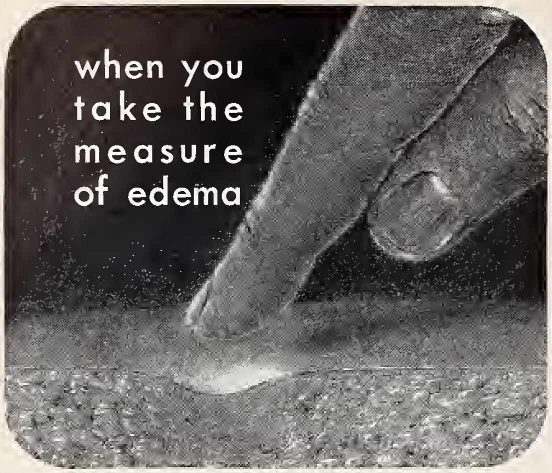
Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs. JAMA 187:664 (Feb. 29) 1964. **2.** Bryans, F. E.: Canad Med Ass J 92:287 (Feb. 6) 1965. **3.** Goldzieher, J. W.: Med Clin N Amer 48:529 (Mar.) 1964. **4.** Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.: Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A.: Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W., Moses, L. E., and Ellis, L. T.: JAMA 180:359 (May 5) 1962. **8.** Kempers, R. D.: GP 29:88 (Jan.) 1964. **9.** Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964. **10.** Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M.: Fertil Steril 16:158 (Mar.-Apr.) 1965. **11.** Flowers, C. E., Jr.: N Carolina Med J 25:139 (Apr.) 1964. **12.** Goldzieher, J. W.: Appl Ther 6:503 (June) 1964. **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.: Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

norethindrone—an original steroid from
SYNTEX
LABORATORIES INC., PALO ALTO, CALIF.

Norinyl® tablets
(norethindrone 2 mg c̄ mestranol 0.1 mg.)

for multiple contraceptive action



. . . introduce your patient to

aquaTag®

(BENZTHIAZIDE)

AQUATAG (Benzthiazide) is a potent, orally active, nonmercurial, diuretic agent. It is effective orally in producing diuresis in edema states, where it is therapeutically comparable to mercurials given parenterally. AQUATAG (Benzthiazide) is mildly antihypertensive in its own right and enhances the action of other antihypertensive drugs when used in combination.

DIURETIC ACTION: Clinically, the oral administration of AQUATAG (benzthiazide) results in diuretic activity within two hours with maximal natriuretic, chloruretic, and diuretic effects occurring during the fourth, fifth and sixth hours. Maintenance of response continues for approximately 12 to 18 hours. Acidosis is an unlikely complication since therapeutic doses of AQUATAG (benzthiazide) do not appreciably increase bicarbonate excretion. Edematous patients receiving 50 mg. of AQUATAG (benzthiazide) daily for five days developed a maximal increase in the rate of sodium excretion on the first day, and maintained this high rate until depletion of excessive body stores of sodium.

In congestive heart-failure patients, AQUATAG (benzthiazide) produced the same weight loss, during a 48-hour treatment period as did a maximally effective dose of hydrochlorothiazide.

DOSAGE: Diuresis, initially 50 to 200 mg.; maintenance 25 to 150 mg., daily. Hypertension 50 to 100 mg. initially, adjusted to 50 mg. t.i.d. or downward to minimal effective dosage level.

WARNINGS: Use with caution in the presence of renal disease as azotemia may be precipitated or increased. In patients with advanced hepatic disease, electrolyte imbalance may result in hepatic coma. Dosage of coadministered antihypertensive agents should be reduced by at least 50%. In cases of suspected electrolyte imbalance, serum electrolyte determinations should be performed and imbalance, if any, corrected. Stenosis or ulcer of small intestine have been reported with coated potassium formulas, and surgery has been required and deaths have occurred. Based on surveys of both United States and foreign physicians, incidence of these lesions is low and a causal relationship in man has not been definitely established. Until further experience has been obtained, the use of the drug in pregnant patients should be weighed against possible hazards to the fetus.

CONTRAINDICATIONS: AQUATAG (benzthiazide) is contraindicated in progressive renal disease or dysfunction including increasing oliguria and azotemia. Continued administration of this drug is contraindicated in patients who show no response to its diuretic or antihypertensive properties. Severe hepatic disease is a relative contraindication. (See "Warnings" above.)

PRECAUTIONS AND SIDE EFFECTS: Electrolyte imbalance with hypokalemia (digitalis toxicity may be precipitated), hypochloremic alkalosis and hyponatremia may occur.

Patients with cirrhosis should be observed for impending hepatic coma and hypokalemia. Other reactions may include blood dyscrasias, hyperuricemia and gout, nausea, jaundice, anorexia, vomiting, diarrhea, dizziness, paresthesia, photosensitivity and headache. Hepatic fetor, tremor, confusion and drowsiness are signs of impending pre coma and coma in patients with cirrhosis. Insulin requirements may be altered in diabetes. AQUATAG (benzthiazide) should be used with caution post-operatively as hypokalemia is not uncommon. Potassium supplementation may be advisable pre- and post-operatively. There have been occasional reports of thrombocytopenia, leukopenia, agranulocytosis, aplastic anemia and precipitation of acute pancreatitis or jaundice.

Before prescribing or administering, read the package insert or file card available on request.

Available as 25 or 50 mg. scored tablets.

Request clinical samples and literature on your letterhead.

S.J. TUTAG
& COMPANY
Detroit, Michigan 48234

Adverse Reactions to LSD

What kind of person takes LSD without medical supervision? Does he really suffer as many ill effects as have been claimed?

Reporting on what they believe to be one of the largest groups of LSD-related adverse reactions studied to date, investigators at the University of California, Los Angeles, describe 70 persons treated after unsupervised LSD administration. The report appears in the August 8 *Journal of the American Medical Association.*

The patients were "predominantly single, white, male, and young (average age, 21)," the report said. Most were from the Los Angeles area, and most were either unemployed or students. All were treated during the seven-month period from September 1965 to last March.

In every case, the victim experienced one or more severe reactions, such as anxiety, depression, or confusion, after the LSD's effects should have worn off. More than half were admitted to the UCLA Neuropsychiatric Institute after receiving emergency treatment. Even in this facility, designed for short-term treatment, most hospitalized patients remained for more than a month.

The authors say they share general concern over what appears to be a rising number of LSD-related disabilities. The 70 cases treated at UCLA constituted 12 per cent of the Institute's patients during the seven months. Prior to mid-1965, an LSD case there was a rarity, the authors said.

Patient numbers didn't decrease when the new Federal Drug Abuse Control amendments went into effect last February. In fact, March was the clinic's busiest month for LSD cases.

Forty per cent of the patients said they had taken other drugs within six weeks of the time they received treatment for LSD reactions. Thirty-six per cent had histories of chronic marijuana use. On the other hand, another 40 per cent had no history of drug usage. Thirty-seven per cent had received previous psychiatric treatment.

Few of the patients had police records, but a third were unemployed. (It was not determined whether the patients stopped working before or after taking LSD.)

"One former disc jockey said that he had lost his employment after using LSD and had no ambition to start work again," the authors said.

A law student said that LSD had opened new vistas to him. "He had 'a perspective of the whole world now' and his legal studies were very dull and uninteresting by comparison," the report said.

The authors noted that none of their patients were "professional-class" persons, in contrast to an earlier report, which said LSD "seems to be mainly used by professionals, intellectuals or other middle-class people."

(Continued on Page 27)

Terrastatin®
Capsules
oxytetracycline 250 mg., nystatin 250,000 units
For Oral Suspension
oxytetracycline 125 mg., nystatin 125,000 units/5 cc.

Contraindicated: In individuals hypersensitive to oxytetracycline or nystatin.

Warning: Reduce usual oral dosage and consider antibiotic serum level determinations in patients with impaired renal function.

Use of oxytetracycline during the last trimester of pregnancy, neonatal period and early childhood may cause discoloration of developing teeth.

During treatment with tetracyclines, individuals susceptible to photodynamic reactions should avoid direct sunlight; if such reactions occur, discontinue therapy.

Note: With oxytetracycline, phototoxicity is unknown and photoallergy very rare.

Precautions: Use of broad-spectrum antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Where such infections occur, discontinue oxytetracycline and institute specific therapy. Increased intracranial pressure in infants is a possibility. Symptoms disappear upon discontinuation of therapy.

Adverse Reactions: Nausea, diarrhea, glossitis, stomatitis, proctitis, vaginitis and dermatitis, as well as reactions of an allergic nature, may occur but are rare.

Supply: Terrastatin Capsules: oxytetracycline, 250 mg. and nystatin, 250,000 units. Terrastatin for Oral Suspension: oxytetracycline, 125 mg. and nystatin, 125,000 units per 5 cc. (when reconstituted).

More detailed professional information available on request.

Science for the world's well-being®
Pfizer
Since 1849
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
New York, New York 10017

Report Released on Use of Seat Belts

Two-thirds of the people who have seat belts use them during highway driving, a California study showed. However, in town, only one-third of them used their belts.

Dr. Paul Joliet, Chief of the Public Health Service's Division of Accident Prevention, which supported the study, said:

"Many more motorists need to be aware of the great importance of wearing seat belts whenever they ride in cars. All the research we have supported shows that collisions, even at low speeds, can produce severe injuries to occupants. Seat belts can lessen the severity of injuries."

The study, conducted by Dean Manheimer of the Family Research Center in the California Department of Public Health on a group of 1,850 Oakland drivers, found that 28 per cent of the drivers interviewed owned seat belts.

"The big need now," said Dr. Joliet, "is to get everyone in the habit of using belts all the time. We could save as many as 5,000 lives and spare a quarter million hospitalizations per year if everyone wore seat belts."

Adverse Reactions to LSD

(Continued from Page 24)

There were, however, 10 businessmen in the group treated, and three housewives.

Since there are no data on numbers of LSD users or the frequency of the drug's use, it is difficult to determine whether many serious side effects go unreported, the authors said.

How do the investigators know that their patients' symptoms were caused by LSD and not by some other cause, and that LSD consumption was just a coincidence?

"We cannot prove a causal relationship, but we can say several things. First, the symptoms of anxiety, depression, suspiciousness, and hallucinations are among those commonly reported after experimental administration of LSD.

"Second, the patients themselves usually attributed the symptoms to the LSD, particularly when they had had a previous (LSD) experience. A typical comment was, 'It was like this before on LSD but I got over it. I can't now; this is a freak trip.' "

LSD is largely gone from the brain at about the same time the adverse mental effects begin, the report said, so delayed reactions may be explained "perhaps on the basis of some triggering chain of events set off by the LSD itself. Symptoms which first began following (the taking of) LSD may recur months later in their original intensity."

The authors are J. Thomas Ungerleider, M.D., Duke D. Fisher, M.D., and Marielle Fuller, all of the Psychiatry Department, University of California, Los Angeles, Center for Health Sciences.

MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis–a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect–metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'–an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase–it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic–an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9,10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin–effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

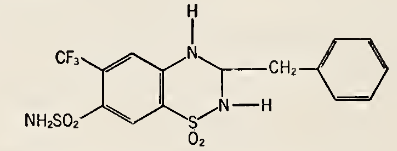
Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: 1. Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



Naturetin®

SQUIBB BENDROFLUMETHIAZIDE
to reduce excess fluid
or high blood pressure

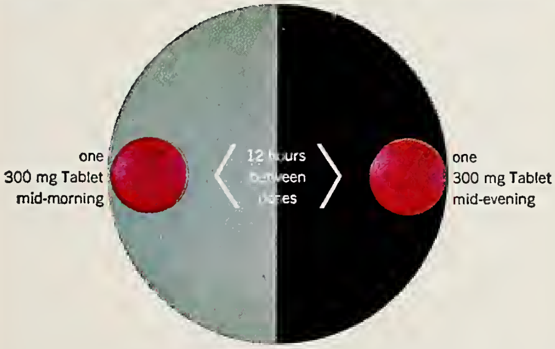
SQUIBB 'The Priceless Ingredient' of every product is the honor and integrity of its maker.

why wonder about a drug when you know

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE

is effective b.i.d.



It's made for b.i.d.

Effective in a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill—when the offending organisms are tetracycline-sensitive.

Contraindication—History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive systemic accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort.

Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York
417-6—4076

Lederle

The discomforts of

DIARRHEA
MUCOUS COLITIS
DIVERTICULITIS
SPASTIC URETERITIS
BLADDER SPASM

are relieved by
direct musculotropic action
with.....

Trocinate®
BRAND THIPHENAMIL HCl

Available in 100 milligram pink sugar-coated tablets.

The high therapeutic index permits dosage sufficient to relieve spasm promptly.

Administer 4 tablets every 4 hours until relief is constant, then adjust maintenance dosage.

Trocinate *BRAND* THIPHENAMIL HCl

Directly relaxes smooth muscle spasm
Combats hypermotility
Non-mydriatic, may be used in glaucoma

Sixteen years of clinical use, with absence of untoward effects, has established the safety and effectiveness of Trocinate.

Trocinate is metabolized in the body and completely eliminated, which is a safety factor. Dosage must be sufficient to maintain the therapeutic blood level.

DISPENSED IN BOTTLES OF
100, 250 AND 2000 TABLETS

Literature and samples sent upon request

WM. P. POYTHRESS & CO., INC.
RICHMOND, VIRGINIA
Manufacturers of ethical pharmaceuticals since 1856

Medical Teachers Praise Research News

Newspapers, magazines, radio and television perform an important service by distributing science news to the public, according to a survey of faculty members at the University of Wisconsin Medical Center.

The majority of medical teachers who replied said they:

1. Consider it important for the public to have a chance to read medical science news in the mass media.

2. Often get scientific information themselves from public news sources.

Asked, "In your opinion, how important is it that the public have an opportunity to read stories published in the popular media about current medical research generally?" 89 per cent of the responding faculty members answered "very important" or "somewhat important." The remaining 11 per cent felt that it makes little or no difference whether the public knows about research.

Medical research news is one way to keep the public informed about how money given to medical research is being spent, about half of these answering the questionnaire pointed out. Another 20 per cent said the public has an interest in medical research news, regardless of the money in question.

Mass media medical research news promotes better community health and also increases public understanding of what research is all about, 17 per cent of the teachers said. The above statements were in answer to a question as to whether it was important for the public to read medical research news, and if so, why.

Fourteen per cent of the faculty members said it is not important for the public to read about medical research because readers do not have the scientific background to understand or properly interpret this type of news.

The survey also sought to determine how much the medical teachers themselves find out about medical developments from the mass media.

Respondents were asked: "Do you ever get information about new research developments within your own specialty from the public media?" Of the 144 replies, 60 per cent said they sometimes get information about their own special medical interests from the mass media. The remaining 40 per cent said they did not.

Ninety-four per cent of the respondents said they sometimes get information about nonmedical science research from the mass media.

Only 21 per cent of the respondents felt that the public understands either "extremely well" or "pretty well" the work being done within their own medical specialty. Thirty-eight per cent, however, felt that the public understands either "ex-

(Continued on Page 33)

Medical Teachers Praise Research News

(Continued from Page 32)

tremely well" or "pretty well" the research being done within science generally.

The survey was prepared and distributed by the Office of Public Information at the University of Wisconsin Medical School, Madison. The authors are Paul Van Nevel, director of public information, and Donald L. Shaw, science writer.

Childbirth Conference Report Is Now Available

The phenomena of the labor of childbirth have baffled scientists since the time of Hippocrates, and causes for initiation of labor remain unknown.

To identify the present state of knowledge concerning the initiation of labor, the National Institute of Child Health and Human Development (NICHD) sponsored an interdisciplinary conference in late 1963. The NICHD is one of the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare.

Proceedings of the three-day conference, held in Princeton, New Jersey, are now available in a 241-page, fully indexed volume entitled *Initiation of Labor.*

The 35 conference participants from the United States and seven foreign countries identified a number of interrelated factors as contributing to the initiation of labor. The exact contribution of each factor to the dramatic event which starts the childbirth process is still elusive, conferees agreed. Hence, the time when both premature and overdue labor can be prevented, when this is in the interest of the mother and her child, is still in the future.

Under the chairmanship of Dr. Claude A. Villee, Jr., Andelot Professor of Biological Chemistry at Harvard Medical School, the conferees discussed the basic physiological properties of uterine smooth muscle; the actions of oxytocin, progesterone, and relaxin; the respective roles of the fetus and the immune phenomena on the induction of labor; and some of the clinical phenomena present at the time of labor.

Research approaches and results discussed at the conference represented the work of scientists and clinicians from many different disciplines: Anatomy, biology, endocrinology, genetics, pharmacology, obstetrics and gynecology, and neonatology—the study of the newborn.

The proceedings, edited by Dr. Jean M. Marshall, Assistant Professor of Pharmacology at Harvard Medical School, includes a summary and over a hundred tables and figures. Copies of the publication, PHS No. 1390, can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 for $1.00.

...but doctor,
I eat like a bird!

IN WEIGHT CONTROL

OBETROL®

Each OBETROL-10 tablet contains: Methamphetamine Saccharate 2.5 mg., Methamphetamine Hydrochloride 2.5 mg., Amphetamine Sulfate 2.5 mg., Dextro-amphetamine Sulfate 2.5 mg. (OBETROL-20 tablets contain twice this potency) Pat. #2748052.

This combination of amphetamines may be useful as an adjunct in the management of certain forms of obesity where an appetite depressant is indicated.

CONTRAINDICATIONS: Hypertension, advanced arteriosclerosis, coronary artery disease, cardiac arrhythmias, peripheral vascular disease, states of undue restlessness, anxiety, excitement, agitated depression, hyperthyroidism, idiosyncrasy to amphetamine, concomitant administration of a monoamine oxidase inhibitor. PRECAUTIONS: Use with caution in individuals with anorexia, insomnia, vasomotor instability, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies, and individuals who are known to be hyperreactive to sympathomimetic agents, or emotionally unstable individuals who are known to be susceptible to drug abuse. Certain monoamine oxidase inhibitors may potentiate the action of Obetrol. SIDE EFFECTS: The most common side effects attended with the use of amphetamines include nervousness, excitability, euphoria, insomnia, dryness of mouth, nausea, vertigo, constipation, and headache. DOSAGE AND ADMINISTRATION: Initial adult dose is one-half to one 'Obetrol-10' tablet daily, preferably one-half to one hour before meals. This may be gradually increased to one 'Obetrol-10' or 'Obetrol-20' tablet one to three times daily as indicated. SUPPLIED: Tablets scored, in bottles of 100, 500, and 1000.

REQUEST SAMPLES AND LITERATURE

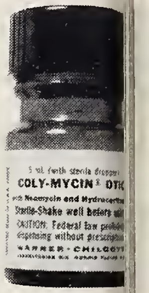
OBETROL PHARMACEUTICALS
Div. of Rexar Pharmacal Corp. Brooklyn, N.Y. 11207

OBETROL PHARMACEUTICALS • BROOKLYN, N.Y. 11207

Dr. ______

Address ______

City ______ State ______ Zip ______



DURING THE "HOT WEATHER EAR" SEASON

MOST CASES OF OTITIS EXTERNA RESPOND

TO MANAGEMENT WHICH INCLUDES THIS...

in all types of otitis externa...
of varying etiology[1]...

Coly-Mycin® Otic as the topical agent was clinicall successful in the treatment regimen of 88.5% of 21 patients in 5 independent studies. Symptomatic re lief was rapid.[2-5] (The 5 studies ranged in succes from 75 to 100%, which is representative of clinica results reported by other investigators.)

removes the bacterial cause
relieves the dermatologic effects
comprehensive

Coly·Mycin® Otic
with Neomycin and Hydrocortisone

Each ml. of Coly-Mycin Otic provides:

Colistin base activity (as the sulfate)	3.0 mg.	for complementary broad-spectrum bactericidal action
Neomycin base activity (as the sulfate)	3.3 mg.	
Hydrocortisone acetate	10.0 mg. (1%)	for anti-inflammatory/antipruritic benefits
Thonzonium bromide	0.5 mg. (0.05%)	for rapid, thorough penetration

Coly-Mycin Otic also contains polysorbate 80, acetic acid and sodium acetate in a buffered (pH 5) aqueous vehicle and thimerosal 0.002% as a preservative.

Buffered to pH 5 to reduce the abnormal alkaline pH which may be favorable to bacterial growth, and to help restore the normal acid pH of the ear canal.[3,4]

Although otitis externa is generally associated with pseudomonal infection, a thorough examination should always be made to discover other causes and/or predisposing factors if any, before specific therapy (such as Coly-Mycin Otic) i adopted as part of the therapeutic regimen.

Recommended dosage: Therapeutic—4 drops t.i.d. Prophylactic—4 drops before and after swimming.

Precautions: Although side effects are not ordinarily encountered with topically applied antibiotics and/or steroids, as with all drugs, some patients may react unfavorably under certain conditions. Should sensitivity or other idiosyncratic reactions occur, Coly-Mycin Otic should be discontinued Overgrowth of nonsusceptible pathogenic organisms is possible, but rare. In the presence of chronic perforated eardrum, the usual precautions recommended in the prolonged topical administration of antibiotic medications should be observed.

Full information is available on request.

References: 1. Mann, P. H.: Current Therap. Res. 6:101, 1964 **2.** Saltzman, M.: Clin. Med. 70:559, 1963. **3.** Ettenger, M. S. Pennsylvania M. J. 66:35, 1963. **4.** Pullen, F. W. II: Eye Ear Nose & Throat Month. *42*:38, 1963. **5.** Jones, E. H., and Mc Lain, P. G.: Eye Ear Nose & Throat Month. *43*:52, 1964. CO GP 6

W|C **WARNER-CHILCOTT**

Warner-Chilcott Laboratories, Morris Plains, New Jersey

California
Medicine

Anesthetic and Recovery Room Records

JOHN B. DILLON, M.D., *Los Angeles*

■ *Anesthetic and recovery room records are important medical documents. In the past they have not been given adequate attention by many anesthesiologists or by most surgeons and other physicians involved in patient care. Anesthetic and recovery room records should be better prepared and better used, for they are an important part of the description of a surgical patient's medical experience.*

IN 1895 HARVEY CUSHING AND E. H. CODMAN introduced the concept of recording anesthesia. Since that time, many kinds of anesthetic records have been devised and employed with varying degrees of acceptance.

The physiologic changes entailed in surgical operation and anesthesia may be so drastic that it would seem self evident today that a detailed record of the course of a patient during these procedures should be kept and studied most assiduously.

Unfortunately, anesthetic records generally are poorly made and rarely referred to later unless there is a serious complication.

What with the medicolegal implications of anesthesia administration and recovery room observation that are developing, hospital staffs would be well advised to have an anesthetic committee as well as a tissue committee. Perhaps a subcommittee of the hospital executive committee could be formed for the purpose. The committee would have the responsibility of reviewing the completeness and adequacy of the conduct of anesthesia *as recorded,* as well as the adequacy and completeness of the recording of recovery room supervision. From experience over many years, it is my observation that, with one or two notable exceptions, anesthetic records that were reviewed because of the inference of negligence left a great deal to be desired.

Not only are anesthetic records important because of the anesthetic procedure described, they can be equally important in relation to the operation for which the anesthetic was given, since a well kept record describes both.

The recovery room record is of great importance to the understanding of the postanesthetic and postoperative course of the patient; and, without such a record, accurately kept, the immediate postoperative condition of the patient is unknown and its influence upon his ultimate course unknowable.

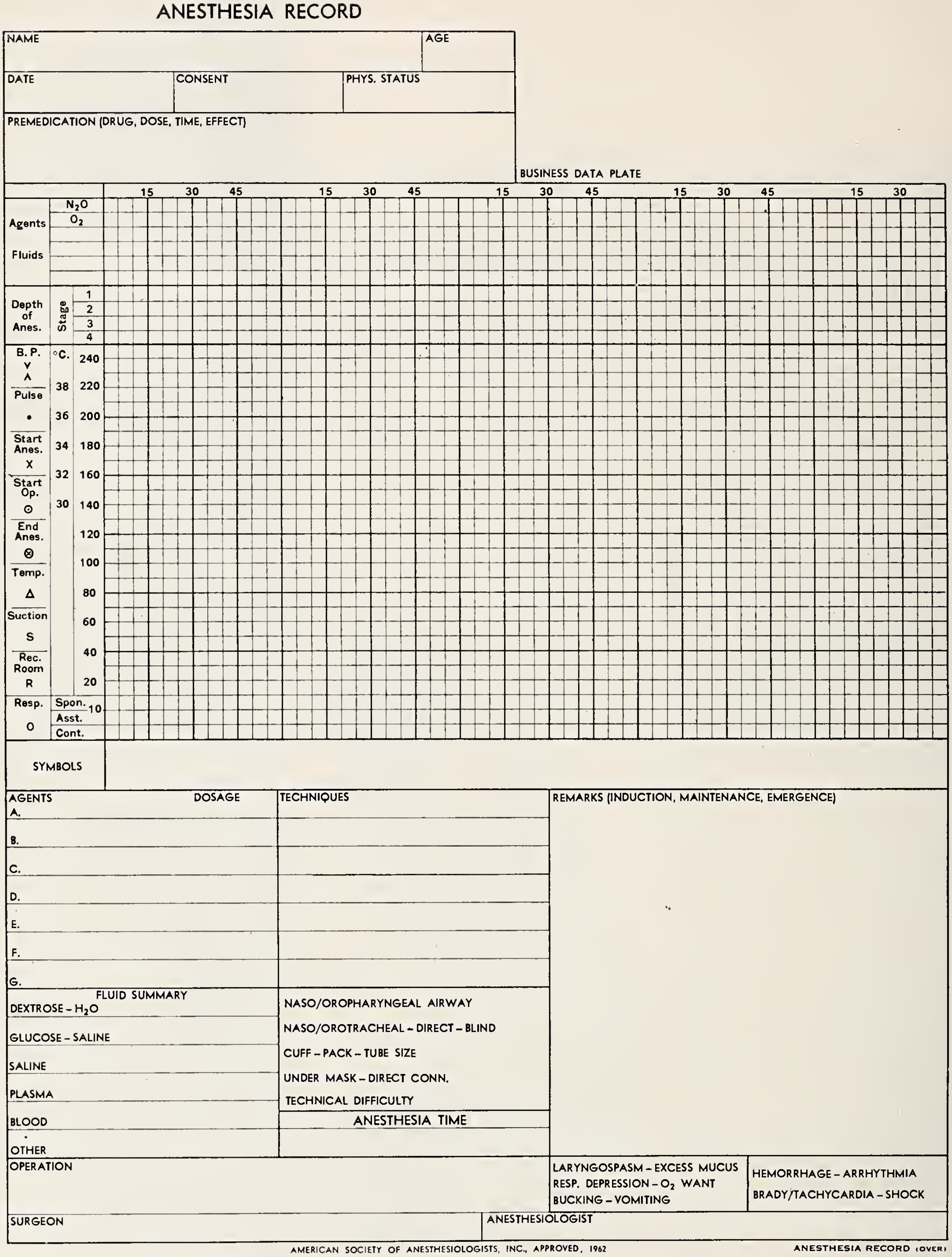
There are many anesthetic record forms in existence, some of them excellent, some very poor. As a basis of comparison, samples of the forms advocated by the American Society of Anesthesiology are shown herewith (Charts 1 and 2). One record is for anesthesia during operation and one is especially modified for the equally important conduct of anesthesia during childbirth. These records, if accurately kept, will describe completely the anesthetic and surgical or obstetrical course during that period. Certainly these records are the minimum that should be accepted. The surgical anesthetic record may not describe some exceptional anesthetic and surgical proceedings adequately, and in such cases more sophisticated

---

From the University of California, Los Angeles, School of Medicine, Department of Surgery/Anesthesiology, Los Angeles.

Submitted 18 March 1966.

Reprint requests to: Department of Surgery, UCLA School of Medicine, Los Angeles, California 90024.



ANESTHESIA RECORD

NAME

AGE

DATE

CONSENT

PHYS. STATUS

PREMEDICATION (DRUG, DOSE, TIME, EFFECT)

BUSINESS DATA PLATE

15 30 45 15 30 45 15 30 45 15 30 45 15 30

Agents N_2O O_2

Fluids

Depth of Anes. Stage 1 2 3 4

B. P. V Λ

Pulse •

Start Anes. X

Start Op. ⊙

End Anes. ⊗

Temp. Δ

Suction S

Rec. Room R

°C. 38 36 34 32 30

240 220 200 180 160 140 120 100 80 60 40 20 10

Resp. O Spon. Asst. Cont.

SYMBOLS

AGENTS DOSAGE

A.

B.

C.

D.

E.

F.

G.

TECHNIQUES

REMARKS (INDUCTION, MAINTENANCE, EMERGENCE)

FLUID SUMMARY

DEXTROSE – H_2O

GLUCOSE – SALINE

SALINE

PLASMA

BLOOD

OTHER

NASO/OROPHARYNGEAL AIRWAY

NASO/OROTRACHEAL – DIRECT – BLIND

CUFF – PACK – TUBE SIZE

UNDER MASK – DIRECT CONN.

TECHNICAL DIFFICULTY

ANESTHESIA TIME

OPERATION

LARYNGOSPASM – EXCESS MUCUS
RESP. DEPRESSION – O_2 WANT
BUCKING – VOMITING

HEMORRHAGE – ARRHYTHMIA
BRADY/TACHYCARDIA – SHOCK

SURGEON

ANESTHESIOLOGIST

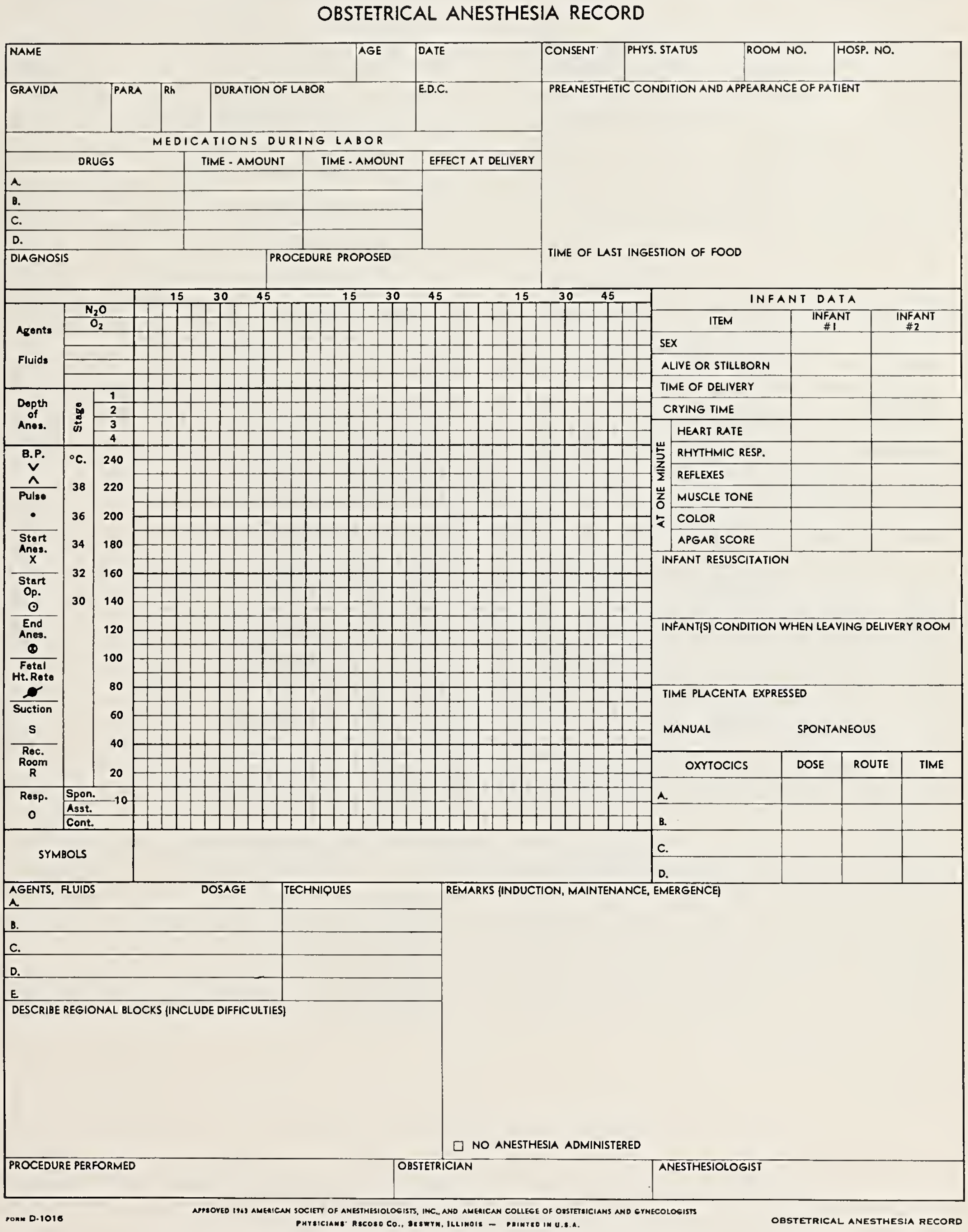
AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., APPROVED, 1962

ANESTHESIA RECORD (OVER)

Chart 1.—Record form for description of clinical anesthesia.

records may be required, but this would be infrequent.

From the patient's point of view, an anesthetic and, indeed, an operation emotionally begin when the surgeon informs the patient of the necessity of the operation and the patient agrees. It is my preference that the preanesthetic evaluation be made as a progress note of the patient's clinical



OBSTETRICAL ANESTHESIA RECORD

NAME	AGE	DATE	CONSENT	PHYS. STATUS	ROOM NO.	HOSP. NO.

GRAVIDA	PARA	Rh	DURATION OF LABOR	E.D.C.

PREANESTHETIC CONDITION AND APPEARANCE OF PATIENT

TIME OF LAST INGESTION OF FOOD

MEDICATIONS DURING LABOR

DRUGS	TIME - AMOUNT	TIME - AMOUNT	EFFECT AT DELIVERY
A.			
B.			
C.			
D.			

DIAGNOSIS	PROCEDURE PROPOSED

15 30 45 15 30 45 15 30 45

Agents N_2O O_2

Fluids

Depth of Anes. Stage 1 2 3 4

B.P. ∨ ∧

Pulse •

Start Anes. X

Start Op. ⊙

End Anes. ⊗

Fetal Ht. Rate

Suction S

Rec. Room R

°C. 38 36 34 32 30

240 220 200 180 160 140 120 100 80 60 40 20

Resp. O Spon. Asst. Cont. 10

SYMBOLS

INFANT DATA

ITEM		INFANT #1	INFANT #2
SEX			
ALIVE OR STILLBORN			
TIME OF DELIVERY			
CRYING TIME			
AT ONE MINUTE	HEART RATE		
	RHYTHMIC RESP.		
	REFLEXES		
	MUSCLE TONE		
	COLOR		
	APGAR SCORE		

INFANT RESUSCITATION

INFANT(S) CONDITION WHEN LEAVING DELIVERY ROOM

TIME PLACENTA EXPRESSED

MANUAL SPONTANEOUS

OXYTOCICS	DOSE	ROUTE	TIME
A.			
B.			
C.			
D.			

AGENTS, FLUIDS	DOSAGE	TECHNIQUES
A.		
B.		
C.		
D.		
E.		

REMARKS (INDUCTION, MAINTENANCE, EMERGENCE)

DESCRIBE REGIONAL BLOCKS (INCLUDE DIFFICULTIES)

☐ NO ANESTHESIA ADMINISTERED

PROCEDURE PERFORMED	OBSTETRICIAN	ANESTHESIOLOGIST

FORM D-1016

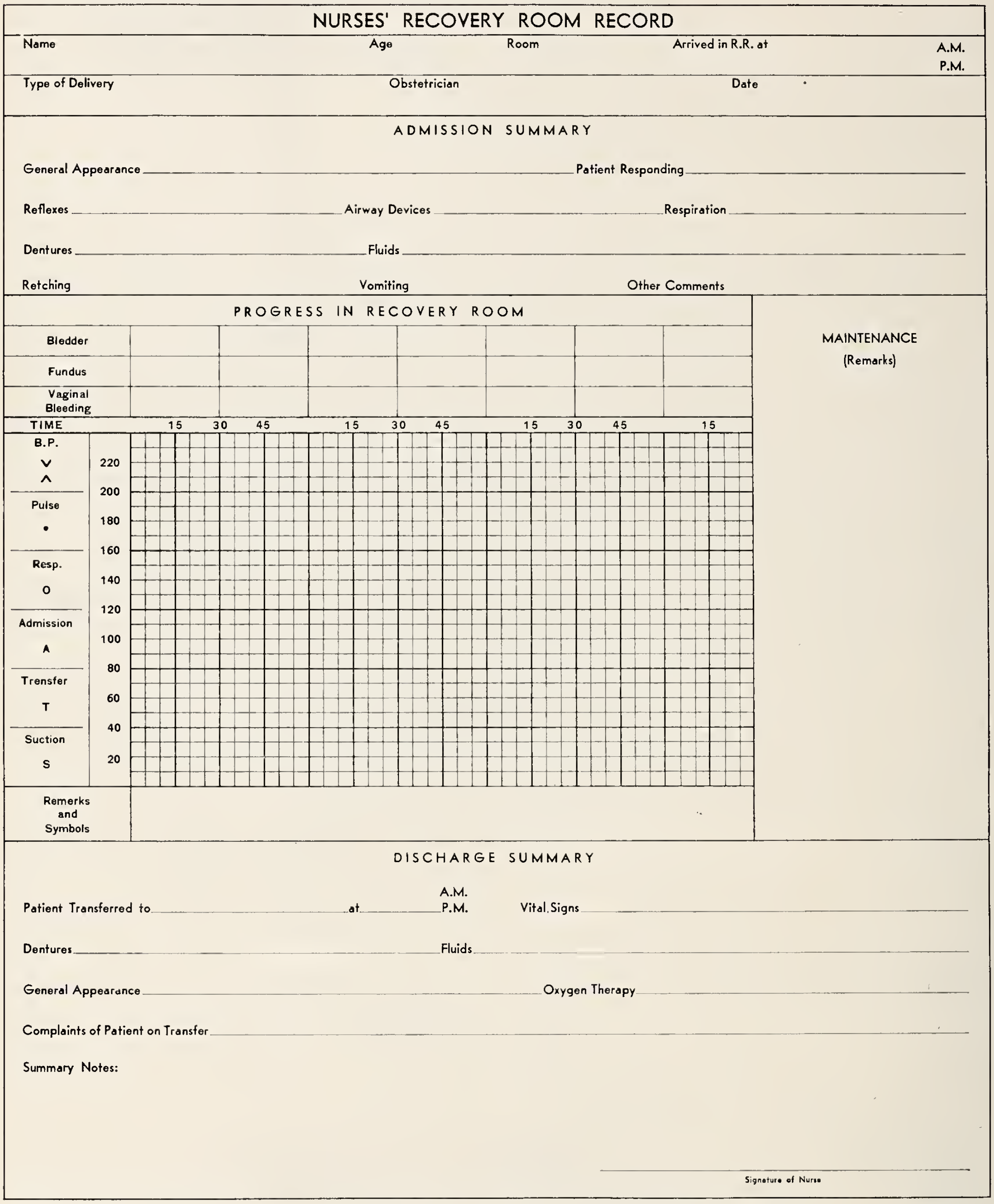
APPROVED 1963 AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., AND AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS
PHYSICIANS' RECORD CO., BERWYN, ILLINOIS — PRINTED IN U.S.A.

OBSTETRICAL ANESTHESIA RECORD

Chart 2.—Record form for description of anesthesia for description for obstetric care.

record. My reason for this is that as a progress note it is seen and read; whereas, if it is on the reverse side of the anesthetic record it is frequently ignored, because it is out of sequence in the patient's record.

The anesthetic record begins when the patient is seen in the induction area, whether it is the patient's room, operating room or delivery room corridor, emergency room, operating room or labor or delivery room. The time that the anesthetist be-



NURSES' RECOVERY ROOM RECORD

Name Age Room Arrived in R.R. at A.M. P.M.

Type of Delivery Obstetrician Date

ADMISSION SUMMARY

General Appearance ____ Patient Responding ____

Reflexes ____ Airway Devices ____ Respiration ____

Dentures ____ Fluids ____

Retching Vomiting Other Comments

PROGRESS IN RECOVERY ROOM

Bladder							
Fundus							
Vaginal Bleeding							

TIME 15 30 45 15 30 45 15 30 45 15

B.P. ∨ ∧

Pulse •

Resp. O

Admission A

Transfer T

Suction S

220 200 180 160 140 120 100 80 60 40 20

Remarks and Symbols

MAINTENANCE (Remarks)

DISCHARGE SUMMARY

Patient Transferred to ____ at ____ A.M. P.M. Vital Signs ____

Dentures ____ Fluids ____

General Appearance ____ Oxygen Therapy ____

Complaints of Patient on Transfer ____

Summary Notes:

____
Signature of Nurse

(D-1016 BACK)

Chart 3.—Chart for description of recovery room care.

gins his ministrations should be noted. This usually is or should be related to the observation of the effects of the premedication, if any, and the observation of the vital signs, pulse, respiration and blood pressure. The time of starting an intravenous infusion, if any, should be noted and the composition and the amount of fluid used should be stated.

If there is a time lapse between the original observation and actual beginning of administration of the anesthetic agent, the time and cause should be noted—for example: "Operating room not ready." Pulse and respiration should be recorded as well as systolic and diastolic blood pressure every five minutes, even though pulse and respiration may be mentally noted continuously via the precordial stethoscope. I would not accept systolic blood pressure estimated by the oscillatory method as valid, although there are times when the palpated systolic pressures may be the only pressures obtainable—but this is rare. Only an unusual event—fully explained in the record—should be acceptable reason for not recording systolic and diastolic blood pressure at five-minute intervals.

Dosages of drugs and manipulations such as intubation and positioning should be noted accurately in relation to time and vital signs.

The use of additional monitors such as body temperature, electrocardiogram and venous pressure should be noted.

The time of the incision or manipulation or other treatment by the surgeon, obstetrician or diagnostician should be included in the record. Frequently in many of the procedures now in use, the length of time taken in preparation of the patient is significant and the period should be accounted for on the anesthetic record.

If changes occur in the vital signs, notes should be made as to probable cause and as to what therapy was applied, if any. Changes in blood pressure and pulse are frequently related to lightening or deepening of anesthesia or to traction reflexes, blood loss and a variety of other phenomena. In such circumstances, notes should be made as to cause and therapy. Continuous observation will show that there is seldom an uneventful anesthetic or surgical, obstetrical or diagnostic procedure and any anesthetic record that shows none is highly suspect.

The time of the termination of the procedure for which anesthesia is given should be noted and the condition of the patient stated.

The record should say what time the patient was turned over to the recovery room personnel or floor nurse and it should include the pulse, respiration and blood pressure at that time, along with notes about anything out of the ordinary in the patient's condition.

The recovery room record or postanesthetic record should be kept with the same detail that the anesthetic record has been kept. There are special recovery room records (Chart 3) but actually the anesthetic record is perfectly satisfactory and is a logical continuation. The records may be combined sequentially on the same record with appropriate notation, or a new sheet may be started.

If the patient's condition demands, the anesthesiologist may well be required to care for him in the immediate postanesthetic period. Exactly when the anesthesiologist may terminate this supervision will always be a matter of judgment on his part. This decision depends upon many factors not part of this discussion. I believe it is desirable that removal of the patient from the recovery room be on order of the anesthesiologist or surgeon, and that an appropriate note should be made in the record.

The anesthetic and recovery room record is a very important document relating a very critical part of any patient's medical care, but its value is only as great as the care and understanding with which it is made. It is suggested that hospital staffs give these records scrutiny to the end of seeing to it that they are of a high order.

Dermatologic Therapy

Point and Counterpoint

PAUL M. CROSSLAND, M.D., *Santa Rosa*

As you know, the theme of the 95th annual session of the California Medical Association is a musical one: "Current Concepts in Therapy—Point and Counterpoint." Perhaps my most apt greeting to you should be: welcome to our musical medical festival. Point and Counterpoint does, in fact, make a most provocative theme for a medical meeting. Devotees of Aldous Huxley will almost certainly relate point and counterpoint to his novel of that name, a novel in which he wove dissident ideas—or tunes, if you will—into a skillful portrayal of English society in the twenties. Huxley pitted one theme against the other. I prefer the classical concept of point and counterpoint in which it is defined as "the conveying of a mass of harmony by means of a combination of melodies."

And I think inevitably of Johann Sebastian Bach, the great master of counterpoint. No musician has ever surpassed him in bringing together and mingling one melody with another to achieve a magnificent and harmonious whole. His musical inventions are fundamentally mathematical and precisely scientific, yet he was able to touch the most formal musical structure with pure joy. His works have so much spiritual warmth that you feel a better person for having listened to them. Certainly *Baroque* music reaches its fullest expression in his hands, for he brought to it a remarkable combination of science and art.

Science and Art in Medicine

The analogy to the practice of medicine is obvious: To reach its fullest expression, medicine, too, requires a skillful combination of science and art. Let us look at our own field of dermatology, a branch of medicine coming rapidly to the forefront, and one which has recently seen great scientific gains. To apply our musical figure, in dermatology, we have a splendid scientific structure—a point and counterpoint of ever more effective scientific themes which we may use and combine.

In my own practice, for example, I use three methods of dermatologic therapy—three themes based on science: *First,* I use topical therapy which consists of appropriate creams, lotions or ointments. *Second,* I use internal medications—antibiotics, steroids and hormones. And for some patients I use mild sedatives with aspirin. *Third,* I use physical therapy consisting of wet dressings, cold or hot quartz ultraviolet light, or, if indicated, x-rays.

These are three good and proven methods that are available today for treating skin disorders. But used alone, or even in combination, they may prove quite inadequate. It is not enough to look at a patient's skin, dash off a prescription and say: "Rub this in three times a day and come back next week." For many patients, such treatment does not make music.

A fourth ingredient is needed—call it "psychological" therapy. Or, to keep our musical simile, our scientific therapy must be administered with art. And the art of medicine depends, in the last analysis, quite simply upon a love and understanding of human beings. The good physician must know that it is not a disease that walks into his office, but a person with a problem. Probably in no other field of medicine is this better demonstrated than in dermatology.

From the Department of Dermatology, Stanford University School of Medicine, Palo Alto.

Chairman's address: Presented before the Section on Dermatology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 1120 Montgomery Drive, Santa Rosa, California 95405.

Thinking About the Patient

Many questions must come to mind when a patient presents himself to the dermatologist. What made him come in the first place? Is he afraid he has cancer? Does he fear some contagious or infectious disease? Is he embarrassed about his appearance and afraid that others will think he has some dreadful condition? Or is he simply looking for relief from discomfort, from itching, burning or pain? What kind of person is he, anyway?

The answers to such questions as these come out best through the taking of a detailed history, and particularly through listening to what the patient says and *how* he says it. It is not hard to spot the neurotic patient, or the vague and evasive man who may be hiding a deeper fear. We are all familiar, too, with the atopic child who is all over the examining room while his mother unconsciously expresses her rejection of him. And who of us has not met the tense executive who is accustomed to giving the orders, and who wants the answers listed, one, two, three. And wants them *now!*

With good fortune, as you take the patient's history and examine him a specific scientific answer comes to mind. And with even better fortune, a bar or two of melody presents itself. Like the good musician, you sense what art you must add to make your patient a whole and harmonious human being. Perhaps he needs assurance—one of the most divine gifts that we can give—or a soft or soothing word. Or he may respond better to a sure and authoritative manner and a direct admonition.

The great William Mayo was not only a fine physician but a master in treating people. He was known to change his manner and method of handling patients completely as he went from room to room in the hospital. With one patient he would be stern, autocratic and quite unsympathetic. With the next, no one could match his kindness and understanding or the words of hope and encouragement he offered. He knew how to reach a person, and he knew what approach would get the best results with each of his patients. Quite simply, he knew the art of practicing medicine. The students he taught never forgot him.

At the time that Mayo taught and practiced, the scope of scientific medicine was limited. With less scientific information to acquire, the student had time to learn the art of practicing medicine from his teacher, either at the bedside or as a preceptee. Today, the emphasis has shifted almost completely, and a student is occupied more and more with learning the scientific aspects of his specialty. And he is given less and less of the art of treating and understanding people—indeed, in some cases he is left almost on his own to come by it.

No one would deny the importance of our recent scientific achievements in medicine. They are all to the good. Twenty—or even 15—years ago, we had to depend too much on guesswork, for lack of positive knowledge. Certainly we welcome the new drugs, the hormones and the great advances in pathology, chemistry and radiobiology—and we cannot begrudge the time needed to learn about them. But even as all work and no play makes Jack a dull boy, all science and no art can turn out a practicing physician with a tremendous gap in his knowledge. He may be ill-equipped to provide the kind of treatment that will best care for people.

Once again I am reminded of Bach. How many of his contemporaries followed the intricate and demanding rules of point and counterpoint and wrote down the correct notes? Certainly there were scores, perhaps hundreds. But because they lacked art and the ability to make music out of the notes they used, they fell short of greatness. No one remembers them: They added little to their chosen field or to the world.

Patients of a New Order

The ascendancy of science and the consequent shift in emphasis in medical training is certainly a major and challenging change in today's medicine. But it is not the only one facing us. Even as we seek to keep art in the practice of medicine, we have to recognize that our own role has changed, too. Gone are the days when the physician was considered second only to God, and when the practice of medicine was regarded with reverence and even awe. The mysteries of medicine are no more. Our scientific advances have been dramatic, often spectacular, and they make for excellent copy. A great many people are now up to the minute on the newest and best, the latest and most sensational treatments. They have read all about them in such popular "medical" journals as *Time, Life* and the *Reader's Digest*. We have to face the fact that today a patient's knowledge of medicine may be quite broad, if very shallow. And this can, indeed, be a dangerous thing. The dermatologist may find himself having to defend his own diagnosis to his patient. For the patient may have already diagnosed his own disease and decided on the treatment he wants.

Quite patently, it is no longer possible to tell a patient what to do and give him no explanation of his condition. Actually, I think this is for the best. I believe in giving the patient the facts pertinent to his case. It's his disease, and he's entitled to know what he can expect from it. The explanation given him should be one that he can understand. And he should be told the prognosis, if he asks for it.

Suppose, however, that you don't yourself know the answers, or the prognosis. Such moments—moments when both science and art desert us—are bound to come to all of us. We may take the most comprehensive history, listen to the man intently, examine him closely, and still get no glimmer. What then?

I think twice before I tell a patient of such a quandary. It is not only my own intelligence that might come into question, but medicine itself. And it can hardly be reassuring to the patient. In such circumstances, it is honest to explain to the patient that his dermatosis has some unusual features, that it could be one of two or three conditions, that in order to establish a diagnosis special laboratory tests are needed, and that, until they are completed, specific treatment should wait.

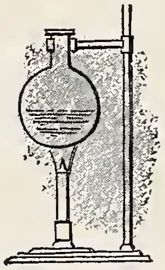
The late Nelson Paul Anderson admitted, after years of successful practice, that he made numerous unnecessary potassium hydroxide preparations for fungi simply because it gave him time to think while he sat at his microscope. I believe this is a highly legitimate, even scientific, method of gaining the time we may need to put our art to use.

The Influence of Medicare

I cannot close without mentioning another major change that is facing us—Medicare. I believe that it presents us with one of the greatest challenges in medical history.

Whatever else it may bring, the arrival of the Federal Government on the field of medical practice is bound to bring a challenge to the physician-patient relationship. And this is the very aspect of medical practice that depends so much upon the understanding—and the art—of the practitioner. We may find bureaucracy coming between us and our patients, and lurking in the door of the consulting room as a third party. Impersonality may be hard to avoid when there are large numbers of persons seeking medical care. But avoid it we must. Now, more than ever before, we need to remember the importance and dignity of the patients we care for.

While we live and practice medicine in this period of challenging and demanding change, and while medicine itself is deep in the throes of this change, there are certain essentials that remain the same. Human beings are still human beings. To care for them and to cure them of their ills can be the most rewarding thing in life. Medicine still demands both science and art. And medicine will continue to demand both science and art—the magic point and counterpoint. As we ourselves may feel after listening to a Bach cantata, let us aim to have our patients leave our hands feeling better people for having come to us.



The Latex Serologic Test For Syphilis

A New Screening Procedure

CHARLES M. CARPENTER, M.D., PH.D., IZABELLA O. KONYA, B.S., AND RONALD A. LE CLAIR, M.S., *Los Angeles*

■ *A new macroscopic screening test for syphilis, the Latex-*STS *test, is extraordinarily simple. After inactivation of the patient's serum for 30 minutes at 56°C the test is performed by mixing the patient's serum with latex particles coated with cardiolipin and a protein fraction obtained from the non-pathogenic Reiter strain of* Treponema pallidum. *Two to three minutes after mixing, the result of the test is observed on a ringed serologic plate. The sensitivity, specificity and reproducibility of the new test are equivalent to those of the qualitative Venereal Disease Research Laboratory tube test. The advantages of the Latex-*STS *are that it can be done in a short time, it is simple and it requires a minimum of laboratory equipment. The coated latex particles are stable for 12 months.*

A MACROFLOCCULATION TEST for syphilis using a cardiolipin-lecithin antigen was described in 1948 by Harris, Rosenberg and Del Vecchio[3] at the Venereal Disease Research Laboratory of the U.S. Public Health Service. Subsequently the test became known as the VDRL test and has been widely used during the past 18 years as a standard routine screening test for syphilis. Three modifications of the test have been developed: (a) A slide test, (b) a qualitative tube test and (c) a quantitative tube test.

Portnoy, Garson and Smith[7] in 1957 introduced a rapid plasma reagin test, the RPR test. The advantage of the test was its use for rapid and economical screening of large numbers of sera. More recently other rapid screening tests have been described, such as the plasmacrit test by Andujar and Mazurek in 1959[1] and the unheated serum reagin test (USR) by Portnoy, Bossak, Falcone and Harris in 1961.[6] The present report is an evaluation of a simple screening test for syphilis, which is designated the Latex-STS.

From the Harry N. Falk Research Laboratory, School of Public Health, Center for Health Sciences, University of California, Los Angeles.

Presented before the Section on Preventive Medicine and Public Health at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Dr. Carpenter died 25 March 1966.

Reprint requests to: Laboratory of Infectious Diseases, UCLA Center for Health Sciences, 10962 Le Conte Avenue, Los Angeles 90024 (Mr. LeClair).

Materials and Methods

Five hundred forty specimens of serum were tested. Ninety were from patients known to have or to have had syphilis which were selected on a basis of darkfield examinations, results of *Treponema pallidum* immobilization (TPI) tests, and on a clinical history of syphilis. They included 20 primary, 20 secondary, 20 latent, 20 late and 10 congenital cases of the disease. Other specimens tested included 100 from the Los Angeles County Health Department obtained for routine premarital and prenatal blood tests and presumed to be non-syphilitic. One hundred specimens were from biologic false positive (BFP) reactors which were selected on a basis of one or more reactive serologic tests, a negative TPI test and a history of disease often associated with BFP reactions. Fifty specimens of serum previously tested in several different laboratories by the Reiter Protein Complement Fixation test (RPCF) and submitted for the TPI test were likewise evaluated. One hundred specimens taken at random as they were received at the TPI laboratory were subsequently tested with the TPI, VDRL and Latex-STS procedures. Ten specimens of spinal fluid were also included in the study.

Non-Treponemal Tests

VDRL *Test* — The qualitative VDRL tube test was performed as recommended by the United States Public Health Service and described in the Manual of Serologic Tests for Syphilis.[4]

Latex-STS—The technique used for the Latex-STS was performed as follows: Serum was inactivated at 56°C for 30 minutes. Two drops of the patient's serum were placed on a ringed serologic plate with a standardized capillary pipette. One drop of antigen,* which consisted of polystyrene latex particles ranging in diameter from 0.15 to 0.4 microns coated with cardiolipin and Reiter protein, was then added and subsequently mixed with the serum, using a wooden applicator. The coated latex particles were suspended in a glycine buffered saline solution, pH 8.2, to which a dye, brilliant green, was added to facilitate reading of the reaction. The plate was gently tilted up and down for two minutes, after which the reaction was observed macroscopically for flocculation.

Treponemal Tests

RPCF *Test*—The Reiter Protein Complement Fixation test (RPCF) was performed in various laboratories before the specimens were submitted for the TPI test.

TPI *Test*—The *Treponema pallidum* immobilization test was performed as described by Nelson and Mayer[5] with the modification recommended by Boak and Miller.[2]

Results

Reactive and weakly reactive tests were observed with approximately equal frequency in both the VDRL and Latex-STS tests. In the evaluation, weakly reactive flocculation tests were considered to be reactive tests.

Sensitivity. The sensitivity of the qualitative VDRL tube test ranged from 40 to 80 per cent depending upon the stage of syphilitic infection. It was 66 per cent for the group of 90 specimens of syphilitic serum. For each type of primary and secondary syphilis it was 80 per cent; for latent, 40 per cent; for late, 70 per cent; and for congenital syphilis, 50 per cent. The sensitivity of the Latex-STS for the group of 90 specimens as a whole was 69 per cent. By categories, the sensitivity was: Primary, 85 per cent; secondary, 80 per cent; latent, 60 per cent; late, 65 per cent; congenital, 40 per cent. (See Table 1.)

Specificity. The specificity was determined on 200 specimens of serum, of which 100 were prenatal and premarital specimens presumed to be non-syphilitic. The other hundred specimens were BFP as determined by the TPI test. The specificity of the VDRL and of the Latex-STS tests on the 200 specimens was 86 per cent for both procedures. The specificity of the VDRL test on the 100 specimens presumed to be non-syphilitic was 100 per cent, and for the 100 BFP specimens, it was 71 per cent. By the Latex-STS procedure it was 97 per cent for the non-syphilitic specimens and 74 per cent for the BFP specimens. A comparison of the results of the VDRL and Latex-STS tests with those of the RPCF test showed an equal agreement of 50 per cent.

The results of the comparative studies on the 100 specimens taken at random as they were submitted for the TPI test were reactive in 29 per cent and non-reactive in 71 per cent. The VDRL tests were reactive in only 36 per cent and non-reactive in 64 per cent. The Latex-STS were reactive in 41 per cent and non-reactive in 59 per cent. The results of the VDRL test were in agreement with the TPI test in 65 per cent and with the Latex-STS in 64 per cent of the cases. The 10 specimens of spinal fluid were non-reactive with the TPI, VDRL and Latex-STS tests.

---

*Provided by the Research Division of the Hyland Laboratories.

Discussion

An evaluation of the results of the Latex-STS on 540 specimens of serum and on 10 spinal fluid specimens with the results of the qualitative VDRL tube test demonstrated the sensitivity, specificity and reproducibility of the two tests to be equivalent. Thus the Latex-STS should become a valuable syphilis control procedure in physicians' offices, in public health laboratories, in blood banks and in international epidemiologic surveys for syphilis because it has several outstanding advantages over the VDRL test. It is rapidly and simply performed with a minimum amount of laboratory equipment. The qualitative VDRL tube test was selected for the comparative evaluation inasmuch as it has greater accuracy than the slide VDRL test. It is possible for one technician to process 300 Latex-STS tests in one day. The number of tests could be increased by substituting a three-minute inactivation time at 62°C. An evaluation with the "short" inactivation time has not been made in this laboratory, however.

It is well known that the non-treponemal tests are non-specific and have a definite limitation in the diagnosis of syphilis. Because of economy and relative ease of performance, however, they are invaluable as screening tests for the infection. Negative STS tests occur in early syphilis and even in a certain proportion of cases of syphilis of many years' duration. Also reactive STS tests are observed in certain non-syphilitic acute and chronic diseases as well as in narcotic addiction and in pregnancy. A significant finding in this evaluation is that only 36 per cent of the 100 specimens submitted for the TPI test were reactive to the VDRL test when retested in this laboratory even though VDRL tests made by the referring laboratory were reported reactive for 95 per cent of the specimens received. Because of its simplicity the Latex-STS may aid in bringing about a greater uniformity of results in interlaboratory non-treponemal tests for syphilis.

TABLE 1.—*Results of a New Screening Test for Syphilis—The Latex*-STS

		Test											
		TPI				*VDRL+*				*Latex-STS*			
		Reactive		*Nonreactive*		*Reactive*		*Nonreactive*		*Reactive*		*Nonreactive*	
Diagnostic Category	*Number of Specimens**	*Number*	*Per Cent*	*Number*	*Per Cent*	*Number*	*Per Cent*	*Number*	*Per Cent*	*Number*	*Per Cent*	*Number*	*Per Cent*
SYPHILIS													
Primary	20	**	......	......	......	16	80	4	20	17	85	3	15
Secondary	20	**	......	......	......	16	80	4	20	16	80	4	20
Latent	20	20	100	0	0	8	40	12	60	12	60	8	40
Late	20	20	100	0	0	14	70	6	30	13	65	7	35
Congenital	10	8	80	2	20	5	50	5	50	4	40	6	60
Total	90	......	......	......	......	59	66	31	34	62	69	28	31
NON-SYPHILIS													
Presumed Non-syphilitic	100	***	......	......	......	0	0	100	100	3	3	97	97
Biologic false positive	100	0	0	100	100	29	29	71	71	26	26	74	74
Total	200	......	......	......	......	29	14	171	86	29	14	171	86
PROBLEM SERA FOR TPI TEST	100	29	29	71	71	36	36	64	64	41	41	59	59
SPINAL FLUIDS	10	0	0	10	100	0	0	10	100	0	0	10	100
SERA SELECTED FOR REPRODUCIBILITY	100					—88 per cent—				—90 per cent—			

---

*A total of 540 specimens tested. The antigen was provided by the Research Division of Hyland Laboratories.

**Diagnosis in primary and secondary syphilis based upon darkfield positive examination or a reactive TPI test.

***TPI tests not performed on these specimens (premarital and prenatal specimens).

+Qualitative VDRL tube test.

REFERENCES

1. Andujar, J. J., and Mazurek, E. E.: The plasmacrit test on capillary blood, Amer. J. Clin. Path., 31: 197-204, 1959.

2. Boak, R. A., and Miller, J. N.: Simple medium for maintaining the viability of Treponema pallidum in the Treponema pallidum immobilization test, Amer. J. Syph., 38:429-433, 1954.

3. Harris, A., Rosenberg, A. A., and Del Vecchio, L. R.: A macroflocculation test for syphilis using cardiolipin-lecithin antigen, J. Vener. Dis. Inform., 29:313-316, 1948.

4. Manual Serologic Tests for Syphilis: United States Public Health Service, 1964.

5. Nelson, R. A., and Mayer, M. M.: Immobilization of Treponema pallidum in vitro by antibody produced in syphilitic infection, J. Exp. Med., 89:369-393, 1949.

6. Portnoy, J., Bossak, H. N., Falcone, V., and Harris, A.: Rapid plasma reagin test with unheated serum and new improved antigen suspension. Pub. Health Reports, 76:933-935, 1961.

7. Portnoy, J., Garson, W., and Smith, C. A.: Rapid plasma reagin test for syphilis. Pub. Health Reports, 72:761-766, 1957.

Electrical Cardioversion

Effectiveness of Quinidine Prophylaxis Following Countershock

ARVIN J. KLEIN, M.D., WILLIAM J. KUZMAN, M.D., ROGER D. STOIKE, M.D.
AND BOBBIE J. BROOKS, M.D., *San Diego*

■ *Direct current countershock was given to 46 patients with chronic atrial fibrillation of diverse causes, with successful conversion in 87 per cent of them. Patients were observed while receiving quinidine prophylaxis, with serial determination of serum quinidine levels, for up to 22 months. Two quinidine preparations were employed, one a long-acting form, in various dosage regimens and both preparations were found to be effective prophylactic agents for maintaining reliable serum quinidine levels. Fifty per cent of patients remained in normal sinus rhythm at three months, 28 per cent at six months and 13 per cent at twelve months.*

DIRECT CURRENT SYNCHRONIZED countershock is a considerable achievement in the treatment of chronic atrial fibrillation and other arrhythmias. Until the introduction of this electrical method for the treatment of ectopic rhythm disorders the major armamentarium included quinidine procainamide and the digitalis glycosides. It had always been recognized that biologic titration with drugs was tedious, and in addition the hazard with quinidine included a 35 per cent incidence of toxicity and a 2 per cent fatality rate.[5] Synchronized precordial electroshock has been the most significant addition to antiarrhythmic therapy since the introduction of quinidine. Notwithstanding the safety and efficacy of countershock, there are still isolated reports of such complications as embolic phenomena, cardiac standstill and ventricular fibrillation.[2,8] To prevent these possible complications, one must anticipate them by proper preparation of the patient, analysis of the ectopic mechanism and awareness of the risks.

Direct countershock is reported in various series as being successful in terminating supraventricular arrhythmia in from 80 to 100 per cent of cases.[4,6,7] Although the arrhythmia may be terminated, maintenance of a normal sinus mechanism depends on the competency of the sinus node and, perhaps, on drug therapy. The necessity, the choice of preparations and the manner of administration of prophylactic quinidine following countershock are questions still unanswered. It would therefore seem important to assess the total value of the countershock therapy in producing long-term sinus rhythm rather than purely the immediate conversion results.

This study has three major purposes: (1) To assess the effectiveness of long-term quinidine maintenance following direct current countershock; (2) to roughly compare the effectiveness of USP Quinidine Sulfate with that of a delayed absorption quinidine preparation*; and (3) to determine if a common denominator of serum quinidine levels exists which contributes to maintaining a sinus rhythm.

From the Department of Medicine, San Diego County University (U.C.) Hospital, San Diego.

Submitted 15 November 1965.

Reprint requests to: 6505 Alvarado Road, San Diego, California 92120 (Dr. Klein).

*Quinidex Extentabs, supplied through the courtesy of A. H. Robins Co., Richmond, Virginia.

TABLE 1.—*Cause of Atrial Fibrillation in 48 Patients*

Cause	*Number of Patients*
Arteriosclerotic heart disease	18
Rheumatic heart disease	15
Thyrotoxic heart disease	2
Pulmonary heart disease	2
Myocardiopathy (Alcoholic)	2
Hypertensive cardiovascular disease	3
Luetic heart disease	1
Miscellaneous combined	5

Materials and Methods

Forty-eight patients, 28 men and 20 women, referred to the Conversion Clinic of the San Diego County University Hospital were the subjects of this study. Forty-seven of them had chronic atrial fibrillation and one had chronic atrial flutter. All had previously been stabilized for cardiac decompensation or recent myocardial infarction. Ages ranged from 28 to 84 years. The causes of arrhythmia in these patients are shown in Table 1.

In general, most patients were considered suitable candidates for countershock. However, some degree of selectivity was practiced in that the suggestions by Hurst[3] were considered relative contraindications. Excluded were patients previously found to be intolerant of quinidine because of idiosyncrasy or cinchonism, patients with atrial arrhythmias precipitated by digitalis toxicity and patients in whom reversion had been attempted more than twice before but had recurrence of arrhythmia despite quinidine prophylaxis.

Most patients were admitted 18 to 24 hours before conversion, and digitalis, diet or diuretics were continued if previously prescribed. All patients were either given sodium heparin, 10,000 units every eight hours, or continued on coumadin if previously prescribed. USP quinidine sulfate (QS) or quinidine long-acting (QX) was started by the ward physician according to a preset schedule. Quinidine sulfate was given in dosage of 200 mg either every six or every eight hours. A 300 mg long-acting quinidine tablet was given either every eight or every 12 hours. The respective medications were given at 10:00 p.m. the evening before the procedure and again at 6:00 a.m. before the conversions, which were generally performed at 7:30 a.m.

On the morning of the procedure an infusion was started of 1,000 ml of 5 per cent dextrose in water containing 40 mEq of potassium chloride and 10 mg of sodium heparin. On occasion 10 units of regular insulin was added to the infusion if borderline digitalis intoxication was suspected. A serum quinidine level was drawn at the time of the infusion and measured fluorometrically by the method of Gelfman and Seligson.[1] Serum concentrations are reported as micrograms per milliliter (quinidine base comprises 83 per cent of quinidine sulfate).

All conversions were performed in the recovery room of the operating suite. Patients were premedicated with 100 mg sodium pentobarbital or 500 mg chloral hydrate the previous evening and 100 mg meperidine with 0.4 mg atropine one hour before the procedure. Anesthesia was administered to all patients, the agent used being intravenous sodium thiopental.

Direct current countershock was delivered with the Lown Cardioverter (American Optical Company). In 35 patients the electrode paddles were applied to the right third interspace and left midaxillary line. A disc paddle was alternately used posteriorly at the left scapular tip in many instances where the left atrium was presumed to be large. The synchronizer was present for a zero delay, and a stepwise increase in capacitor discharge, starting with 150 watt seconds and rising to a maximum 400 watt seconds, was given. In no case were more than four shocks given to any patient. Following the procedure, patients were discharged either the same day or the next morning and advised to continue their prescribed quinidine. They were reevaluated in one week and then observed at monthly intervals thereafter, at which time blood quinidine levels and electrocardiograms were obtained.

Results

There were 57 conversion attempts on 46 patients* and there were 50 successes in 40 patients and seven unsuccessful attempts on six patients. Thus, 88 per cent of the conversion attempts were successful and 87 per cent of patients reverted to a normal sinus mechanism. (Interestingly, the seven unsuccessful conversions (Table 2) were in relatively young persons with severe forms of heart disease such as cardiomyopathy, hemochromatosis or rheumatic calcified annulus.)

---

*Two of the original 48 patients converted spontaneously on long-acting quinidine every 12 hours, one with serum quinidine levels of 1.0 mcg and the other with 2.8 mcg per ml. Both patients had prolonged follow-up and although the quinidine was discontinued from three to six months following conversion a normal sinus rhythm was maintained (Table 3). It should be noted that the table lists one conversion attempt for each patient. These are drug reversions and do not enter into the final analysis.

TABLE 2.—*Unsuccessful Conversions**

Case	*Age Sex*	*Cause*	*Duration of Arrhythmia*	*Date of Conversion*	*Quinidine Level (mcg per ml)*	*Drug and Dosage*	*Number of Conversion Attempts*
1	48 M	Cardiomyopathy LBBB, AF	10 years	5/64	4.2	QX 300 mg q12h	1
2	44 F	Calcified annulus RHD, MR, MS, LVH, AF	6 months	4/64	5.4	QS 200 mg q6h	1
3	55 M	? Cardiomyopathy ASHD, AF	8 years	5/65	1.2	QX 300 mg q12h	1
4	59 M	RHD, MR, LVH, AF	4 years	1/64 2/64	6.0 2.6	QS 200 mg q6h QX 300 mg q12h	2
5	68 M	Hemochromatosis ASHD, AF	8 years	3/64	2.0	QS 200 mg q6h	1
6	46 M	HCVD, LVH, AF	4 years	4/65	3.4	QS 200 mg q6h	1

---

*Quinidine levels represent those at the time of conversion. ASHD=arteriosclerotic heart disease; RHD=rheumatic heart disease; LVH=left ventricular hypertrophy; LBBB=left bundle branch block; HCVD=hypertensive cardiovascular disease; MR=mitral regurgitation; MS=mitral stenosis; M=male; F=female; QX=Quinidine Extentabs; QS=USP Quinidine Sulfate; AF=atrial fibrillation.

In the 46 cases in which conversion was attempted, a successful conversion was considered to be one where a normal sinus mechanism was maintained for at least one week. All patients were followed for periods varying between one week to 22 months. However, seven patients were lost to follow-up after one month. Thirty-three patients (72 per cent) remained in normal sinus rhythm at one month, 23 (50 per cent) at three months, 13 (28 per cent) at six months and six (13 per cent) at from 12 to 22 months.

Quinidine long-acting (QX) was given to 34 patients. When the dosage was 300 mg every 12 hours the average serum quinidine level was 2.4 mcg per ml. When it was given every eight hours the average serum level was 5.8 mcg per ml. At the time of conversion the mean serum level was 3.3 mcg per ml for all dosage regimens (Table 4).

USP quinidine sulfate (QS) was given to 17 patients. When the dose was 200 mg every six hours the average serum quinidine level was 3.6 mcg per ml. When 200 mg was given every eight hours the average serum level was 2.7 mcg per ml. One patient (Case 7, Table 5) was given 400 mg every six hours and the serum level was 8 mcg per ml at conversion. Eleven specimens were obtained at the time of conversion with an average serum level of 4.2 mcg per ml for all dosage regimens (Table 5).

In the seven unsuccessful conversion attempts QX was given every 12 hours to three patients and an average serum quinidine level of 2.7 mcg per ml was noted. QS was given at six hour intervals in four instances and the average serum level was 4.2 mcg per ml (Table 2).

In four patients quinidine intolerance developed, with symptoms of cinchonism—three on QX and one on QS. One patient (Case 12, Table 5) died with normal sinus rhythm four months following quinidine discontinuation. Two patients

TABLE 3.—*Spontaneous Conversions in Two Patients**

Case	*Age Sex*	*Cause*	*Duration of Arrhythmia*	*Date of Conversion*	*Quinidine Level at Conversion (mcg per ml)*	*Quinidine Maintenance Levels (mcg per ml)*	*Drug and Dosage (mg)*	*NSR (Months)*	*Number of Conversion Attempts*	*Comments*
1	58 M	RHD, AI, LVH, AF	5 mos.	4/64	1.0	3.2 3.4 2.2 7.2	QX 300 q12h	9	1	
2	73 F	Thyrotoxic ASHD, AS, LVH, AF	2 yrs.	4/64	2.8	2.0	QX 300 q12h	18	1	Quinidine discontinued 7/64.

---

*The quinidine levels represent those at the time of conversion and maintenance levels are those at intervals during follow-up. RHD=rheumatic heart disease; ASHD=arteriosclerotic heart disease; AI=aortic insufficiency; AS=aortic stenosis; LVH=left ventricular hypertrophy; AF=atrial fibrillation; QS=USP Quinidine Sulfate; QX=Quinidine Extentabs; M=male; F=female.

TABLE 4.—*Data on 26 Patients Given 300 mg Quinidine Extentabs (QX)**

Case	Age	Sex	Cause	Duration of Arrhythmia	Date of Conversion	Quinidine Levels Conversion (mcg per ml)	Quinidine Level at Conversion (mcg per ml)	Drug and Dosage (mg)	NSR (Months)	Number of Conversion Attempts	Comments
1	57	F	RHD, MS, AI, LVH, AF	5 years	2/64	3.2	6.6; 4.2 2.5	QX q12h QX q8h QX q12h	2	2	Intolerant. Refibrillated 4/64.
2	78	F	ASHD, Atrial Flutter	1 month	5/65	6.8	4.3	QX q8h QX q12h	1	1	
3	64	F	ASHD, MR, AI, LVH, MI, AF	3 years	9/64	5.4	2.3	QX q8h QX q12h	1	1	Intolerant. Refibrillated 10/64. Expired 1/65—CVA.
4	62	M	ASHD, MI, PE, AF	2 years	6/64	3.6	5.4	QX q12h	1	1	
5	78	M	ASHD, AS, AI, MR, AF	4 months	6/64	1.6	1.8	QX q12h	1	1	Refibrillated 7/64.
6	69	F	ASHD, MR, LVH, AF	9 years	8/64 8/64	2.2 2.3	5.9; 6.8	QX q12h QX q8h QX q12h	1	2	Refibrillated 9/64.
7	41	F	CM, AF	2 years	2/64	2.2	3.0	QX q12h	1	1	
8	57	F	RDH, MS, MR, LVH, AF	3 months	2/64	2.1	4.2; 3.1 2.3	QX q8h QX q12h	6	2	
9	36	M	RHD, MS, AI, LVH, AF	2 years	2/64	1.4	1.8; 1.8	QX q12h	4	2	
10	56	M	ASHD, Lues, AI, LVH, AF	3 months	2/64 3/64	2.4 1.6		QX q12h QX q12h	2	2	
11	36	F	RHD, MS, AF	7 months	5/65	1.0	1.0; 3.8	QX q12h	2	1	
12	64	M	Thyrotoxic AF	1 year	5/65	1.6	1.8; 2.4 2.4	QX q12h	3	1	
13	57	F	RHD, MS, MR, LVH	6 years	3/64	2.0		QX q12h		1	Died 12 hours. Autopsy—pulmonary embolus.
14	61	M	ASHD, Emph., AF	1 year	3/64	3.8	1.6; 4.8 2.8; 3.4 2.6; 4.9 2.9; 1.8	QX q12h	22	1	QX discontinued 11/64. NSR 8/65.

15........44	M	RHD, MR, MS, LVH, AF	8 months	8/64	1.1		QX q12h			
						6.6; 7.2	QX q8h	6	3	
				2/65		8.8				
16........66	M	ASHD, Emph., MI, LVH, AF	6 months	11/64	2.6		QX q12h	7	3	QX discontinued 5/65. Refibrillated 5/65.
				5/65		5.6; 2.9				
				6/65				1		
17........77	M	ASHD, MR, LVH, AF	11 months	2/65	3.0		QX q12h			
						3.8; 1.4		4		
						1.9; 2.2			2	
				5/65	1.4		QX q12h	2		
18........65	F	RHD, MS, MR, AI, LVH, AF	6 months	8/64	4.0		QX q12h			
						4.2; 5.2		13	1	
						4.2; 4.4				
						4.9; 5.6				
19........71	F	ASHD, MR, AF	2 years	2/64	3.0		QX q12h			QX discontinued 6/64. Refibrillated 2/65.
						3.8; 5.2		11	3	
						2.8; 2.6				
						3.8				
				2/65	3.8			1		
				3/65	3.2					
20........55	F	RHD, AI, MR, LVH, AF	2 years	8/64	2.3		QX q12h	3		Intolerant. QX discontinued 9/64. Refibrillated 11/64. Conversion without QX unsuccessful.
						5.0			2	
				11/64			none			
21........69	F	ASHD, MR, LVH, AF	9 years	8/64	2.2		QX q12h	1		
						5.9; 6.8	QX q8h		2	
				9/64	2.3		QX q12h	1		
22........78	M	ASHD, MR, LVH, MI, AF	1 month	8/64	1.8		QX q12h	2	1	Died 10/64—CVA.
						1.9				
23........53	F	RHD, LVH, AS, AI, AF	5 years	4/64	1.6		QX q12h			
						2.6; 1.8		5		
				8/64	5.0		QX q8h			
						4.0				
				9/64	4.4			1		
24........28	M	RHD, AI, LVH, AF	6 years	3/64	8.0		QX q8h			
						2.4; 1.4	QX q12h	12	1	
						2.8; 2.4				
						3.3; 4.2				
						1.8; 4.2				
						2.8; 1.4				
25........65	M	ASHD, AF	7 years	2/65	2.0		QX q12h	1	1	
26........51	M	ASHD, AF	2 months	4/64	6.0		QX q8h	18		QX discontinued 4/64.

---

*NSR is the period of follow-up with normal sinus rhythm. ASHD=arteriosclerotic heart disease; RHD=rheumatic heart disease; Emph.=emphysema; PE=pericardial effusion; MR=Mitral regurgitation; MS=mitral stenosis; AI=aortic insufficiency; MI=myocardial infarction; AS=aortic stenosis; LVH=left ventricular hypertrophy; AF=atrial fibrillation; CVA=cerebrovascular accident; CM=cardiomyopathy; M=male; F=female.

(Cases 1 and 20, Table 4) reverted to atrial fibrillation two and three months, respectively, following discontinuation of quinidine.

There was one death in this series presumably attributable to conversion (Case 13, Table 4). The patient had severe mitral stenosis with insufficiency, atrial fibrillation of six years' duration and previously unsuccessful attempts at quinidine conversion. She died 12 hours following successful conversion, and at necropsy old massive organized bilateral pulmonary artery thrombosis was noted. In one patient (Case 9, Table 5) ventricular tachycardia developed with the first shock. Subsequently the heart reverted to normal sinus rhythm with an additional discharge.

In four patients quinidine was discontinued either immediately or up to one year following conversion. One patient (Case 16, Table 4) remained in normal sinus rhythm for eight months while on quinidine and reverted to atrial fibrillation within one week following discontinuation. Two further attempts at conversion, one without quinidine, were unsuccessful. At the time this report was being written, three patients (Cases 14 and 26 in Table 4 and Case 1 in Table 3) had gone nine, 18 and 15 months, respectively, without quinidine prophylaxis.

Comment

Our experience with the success of direct current countershock in terminating atrial fibrillation is similar to that of other observers[4-7] in that there appears to be no clear-cut relationship between the age of the patient, the duration of arrhythmia or the ease of conversion. Our experience also confirms the impression of these others that atrial fibrillation secondary to arteriosclerotic heart disease is easiest to terminate while that of rheumatic heart disease associated with left atrial hypertrophy is most difficult. Because it is impossible to predict with any degree of certainty which patients will maintain a normal sinus mechanism, it is our policy to consider all patients with atrial fibrillation as suitable candidates for conversion at least once.

Ninety-two per cent of persons who were given Long-Acting Quinidine on a 12-hour schedule maintained serum quinidine levels between 1 and 5 mcg per ml while 83 per cent of patients given USP Quinidine Sulfate on a six-hour schedule maintained serum quinidine levels of the same magnitude (see Chart 1). Of 23 patients maintaining a sinus rhythm three or more months, 13 were receiving Quinidex Extentabs,® eight were

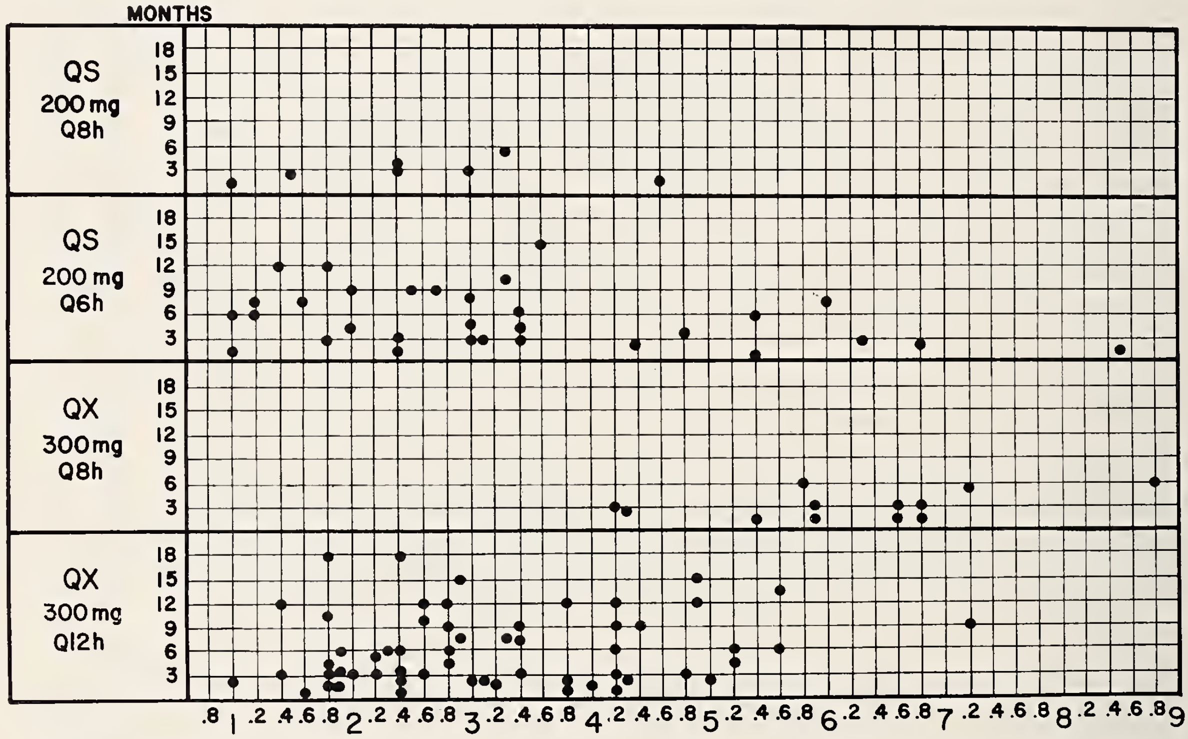


Chart 1.—Serial serum quinidine levels for all dosage regimens of both USP Quinidine Sulfate (QS) and Quinidine Extentabs (QX). The abscissa represents the serum levels in micrograms per millimeter. The ordinate represents the interval following electrical conversion in months.

TABLE 5.—*Data on 14 Patients Given USP Quinidine Sulfate**

Case	*Age*	*Sex*	*Cause*	*Duration of Arrhythmia*	*Date of Conversion*	*Quinidine Level at Conversion (mcg per ml)*	*Quinidine Maintenance Levels (mcg per ml)*	*Drug and Dosage (mg)*	*NSR (Months)*	*Number of Conversion Attempts*	*Comments*
1	53	M	ASHD, Emph., Thyrotoxic, AF	1 year	11/63		1.3; 2.4 3.3	QS 200 q8h	5	1	
2	51	F	RHD, MS, MR, AF	5 years	11/63		3.0; 3.4 1.0; 3.0 2.5; 3.3 1.4; 1.8 0.4	QS 200 q6h	12	1	
3	74	M	ASHD,MR, LVH, AS, AF	2 years	2/64	4.4		QS 200 q6h	1 wk.	1	Refibrillated 1 week. Femoral embolus 2 weeks.
4	84	F	ASHD, RHD, MS, MR, LVH	20 years	3/64	1.6		QS 200 q6h	1	1	Persistent nodal rhythm.
5	66	M	ASHD, MR, AF	2 years	1/64	6.2		QS 200 q6h			
6	75	M	ASHD, MR, AS, MI, LVH	3 years	1/64	7.0	5.4; 6.8 6.3 3.4; 4.8 5.4	QS 200 q6h QS 200 q6h QS 100 q6h	4	1	
7	50	M	HCVD, LVH, MI, AF	1 day	10/64	8.0	1.2	QS 400 q6h QS 200 q6h	5	1	
8	57	F	RHD, LVH, MS, MR, AF	2 years	11/63		1.0; 2.4	QS 200 q8h	3	2	
9	73	F	Thyrotoxic ASHD, LVH, AS	2 years	2/64	2.2		QS 200 q6h	2		Refibrillated 4/64. Ventricular tachycardia with first shock.
10	79	M	ASHD, MR, LVH	6 months	11/63	1.2	1.8; 2.0 1.2; 1.8 2.0	QS 200 q6h	9	1	
11	78	M	ASHD, AF	16 years	4/64	5.4	2.2	QS 200 q6h	1		Refibrillated 5/64.
12	80	M	ASHD, MI, AF	2 years	4/64	1.6		QS 200 q6h	4		Intolerant. Died 8/64. QS discontinued 4/64.
13	57	F	RHD, MS, AI, LVH, AF	5 years	12/63	4.6		QS 200 q8h	2		Refibrillated 2/64.
14	44	M	RHD, MR, MS, LVH, Emph.	3 years	12/63	4.4	8.5; 4.4 3.1; 3.0 3.4; 6.0	QS 200 q6h	8	3	

---

*NSR is the period of follow-up with normal sinus rhythm. ASHD=arteriosclerotic heart disease; RHD=rheumatic heart disease; HCVD=hypertensive cardiovascular disease; Emph.=emphysema; MR=mitral regurgitation; MS=mitral stenosis; AS=aortic stenosis; AI=aortic insufficiency; MI=myocardial infarction; LVH=left ventricular hypertrophy; M=male; F=female.

taking USP quinidine sulfate and two were not receiving quinidine. Quinidex Extentabs® when given 300 mg every 12 hours appeared to be reliable and safe in maintaining adequate serum quinidine levels below toxicity. The ease of administration of a 12-hour schedule as opposed to a six-hour schedule with USP quinidine sulfate is a favorable consideration. In this study we made no attempt to either randomize or accurately compare the effectiveness of the two quinidine forms. As the study progressed the usefulness of the long-acting quinidine preparation became more apparent and it became our prophylactic agent of choice.

The problem of quinidine prophylaxis is only incompletely answered by this study. The maintenance of a normal sinus rhythm depends, among other things, on the competency of the sinus node. This study still leaves unanswered the question of which hearts will remain stabilized without quinidine prophylaxis. Of the 23 patients maintaining a normal sinus mechanism for three or more months, four without quinidine prophylaxis have maintained normal rhythms an additional nine to 15 months. One could then speculate that a good proportion of all patients (perhaps 15 per cent) might receive no additional benefit from quinidine prophylaxis following electrical conversion. Since in only one case in the present study was conversion attempted without quinidine, this might be worthy of a future investigation.

Quinidine has several pharmacologic effects. It inhibits the vagal influence on the sinus node, slows conduction through the myocardium and conducting tissues and decreases myocardial excitability. Because of these various effects on the heart, it would appear beneficial to maintain some permanent "safe" serum quinidine level following the conversion of arrhythmias. However, serious toxic reaction to quinidine is often demonstrated with serum quinidine concentrations greater than 6 mcg per ml.[9] In the present study 50 per cent of patients maintained a normal sinus mechanism for at least three months and 28 per cent for at least six months while receiving quinidine with serum levels less than 5 mcg per ml. It would, therefore, be reasonable to recommend serum quinidine levels of this magnitude for approximately six months after conversion, followed by a watchful waiting period without prophylaxis.

REFERENCES

1. Gelfman, N., and Seligson, D.: Quinidine, A. J. Clin. Path., 36:390-393, 1961.
2. Graf, W. S., and Etkins, P.: Ventricular tachycardia after synchronized direct-current countershock, J.A.M.A., 190:470-472, 1965.
3. Hurst, J. W., Paulk, E. A., Jr., Proctor, H. D., and Schlant, R. C.: Management of patients with atrial fibrillation, Am. J. Med., 37:732-733, 1964.
4. Killip, T.: Synchronized DC precordial shock for arrhythmias, J.A.M.A., 186:1-7, 1963.
5. Lown, B.: Electrical methods for terminating arrhythmias of the heart, Mod. Med., 122-132, 26 October 1964.
6. Lown, B., Amarasingham, R., and Neuman, J.: New method for terminating cardiac arrhythmias; use of synchronized capacitor discharge, J.A.M.A., 152:545-555, 1962.
7. Meltzer, L. E., Aytan, N., Yun, D. D., Ural, M. D., Florentino, P. P., and Kitchell, J. R.: Atrial fibrillation treated with direct current countershock, Arch. Int. Med., 115:537-542, 1965.
8. Rabbino, M. D., Likoff, W., and Dreifus, L. S.: Complications and limitations of direct-current countershock, J.A.M.A., 190:417-420, 1964.
9. Sokolow, M., and Perloff, D. B.: Clinical pharmacology and use of quinidine in heart disease, Progr. Cardiovasc. Dis., 3:316-320, 1961.

Topical Cryotherapy

Use for Relief of Pain and Spasticity

SEDGWICK MEAD, M.D.
AND
MARGARET KNOTT, A.B., R.P.T., *Vallejo*

■ *Cold applications are sometimes of pronounced symptomatic benefit in some rheumatic disorders such as acute myalgia; in the temporary relief of spasticity; in helping to release tight structures in poliomyelitis and allied diseases; and in temporary recovery of energy in multiple sclerosis.*

EVER SINCE the beginning of the scientific revolution in medicine, physicians have fallen into the easy assumption that every kind of treatment they habitually order is based on building stones as solid as the Koch postulates. Even when some hallowed notion gets jostled—like prolonged bed rest after surgical operation, or the necessity of operations like circumcision and tonsillectomy—they tend to be uncritically accepting of many other procedures that they continue to do.

One of these entrenched routines is the use of some form of heat in preparation for other physical measures. The purpose of this article is to indicate an alternate procedure—removal rather than addition of heat to the body. The extreme individualist might even decide to use neither heat nor cold.

Since 1952 in our clinic applications of ice rather than heat have constituted the usual mode of preparation of the patient for further physical treatment. This has been true of both short-term, localized disorders suitable for outpatient care and of long-term, severely involved (rehabilitation) conditions. In contrast to the very little heat that can be conveyed to patients by one diathermy unit and a single whirlpool, we use the principle of heat exchange in the other direction provided by the latent heat entailed in the fusion of about one ton of ice per day.

Theoretical Background

While the literature on thermotherapy is nearly endless (and pretty sterile), that on its counterpart, cryotherapy, is sparse indeed. A group of scholarly studies from Canada and Britain are reported in Volume 17 of *British Medical Bulletin,* January 1961.[1] The entire issue is devoted to the physiologic aspects of cold and the technique of induced hypothermia. The articles on local cooling, vascular effects and the effects on nerve transmission are of particular interest, but the emphasis is on profound change—hypothermia as used in operations on the central nervous system and the heart—and not on the kind of brief chilling used in physical medicine. In the latter technique even the employment of ice baths rarely lowers the core body temperature more than 1°F.[5] In 1951, Wakim, Porter and Krusen[7] plotted the time-temperature curves of skin, muscle and joints when the limb was packed in ice for one hour. The temperature of the internal tissues declined 6°C within 10 minutes of application and fell only 2° to 3°C more by the end of an hour of chilling. After one hour of recovery these tissues still lacked 1° to 2°C of

---

Presented before a Joint Meeting of the Sections on Physical Medicine and Industrial Medicine and Surgery at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Kaiser Foundation Rehabilitation Center, 2600 Alameda Street, Vallejo, California 94590 (Mead).

returning to control temperature. Zaimis, Cannard and Price[9] found that lowering of muscle temperature increases the magnitude and duration of effects of neuromuscular blocking agents. Kelly and Fry[4] found in the excised muscles of the frog that twitch tension increases in both directions from a minimum at 20°C, as the muscle is either warmed or cooled.[4] Brooks, Koizumi and Malcolm[2] found that, in cats, warming depressed reflex activity of the exposed spinal cord. Cold produced a remarkable augmentation of all responses. When chilling reached 20°C, cold block occurred. Intramedullary conduction of impulses was slowed by cooling; synaptic impulses were, however, augmented in amplitude.

Effect on Spasticity

Heat has been used for many years to relax spastic limbs (spasticity is here defined solely as resulting from disease of the pyramidal-extrapyramidal systems so that stretch reflexes are abnormally increased). Heat is not very efficacious for this purpose. By contrast, cold applications are decidedly effective. Decrease in resistance to passive stretch lasts from a few minutes up to 24 hours. Unmasking of spasticity permits strengthening of voluntary mechanisms normally snowed under by undesired reflexes.

The explanation of the mechanism of relief of spasticity must be at present purely speculative. It is possible that cold anesthesia of peripheral sensory end-organs changes the balance of the algebraic sum of facilitatory-inhibitory influences playing on the anterior horn cell in favor of inhibition. Wearing off of the cold anesthesia would then permit return to the previous conditions of spasticity. One observed paradox is that patients with spasticity say they are often worse on cold days.

Joint Restriction in the Rheumatic Affections

The only mechanism suggested for the present is cold anesthesia. Again a seeming paradox may be observed: Patients who have decreased joint mobility on cold, damp days may, nevertheless, be benefited by ice applications. There is, however, a vast difference between cold, damp climate and severe local chilling of the skin and underlying tissues.

It is necessary to separate increase in joint mobility secondary to relief of pain from increase in joint mobility from other mechanisms. In nonpainful restricted joints sometimes observed in the evolution of periarthritis of the shoulder, one must also be sure that adhesions (histological contracture) have not occurred. This can be decided only by gentle passive testing under curarization and general anesthesia. Cold has no effect on histological contracture. One can often demonstrate increase in muscle extensibility, especially of tight hamstring muscles, after cold application in a normal subject.

Relief of Certain Types of Pain

That surface anesthesia—induced either by cold or by drugs—can produce pain relief in certain types of deep-seated pain is incontestably established.[3] Travell and Rinzler[6] used surface block in coronary pain. We once noted striking relief of pain by chilling the anterior thigh with ethyl chloride spray in a young woman who later proved to have metastasis to the femur from carcinoma of the thyroid gland.

Cold anesthesia is quite limited by severe discomfort which develops at the transitional zone between warm and cold tissues and ordinarily is not suitable for chronic intractable or diffuse pain syndromes.

Techniques of Application

For relaxation of hands and feet, immersion in a mixture of ice and water is suitable. Following immersion there will nearly always be an increase in spasticity of the flexors. To relax these further, we suggest that towels dipped in ice water, which is at approximately 15°C, be put directly over the groups which are tight or limited in range. For best results it is advisable to move the part through the range you wish to obtain while the cold towel is on the part. If there is tightness or spasticity of both flexors and extensors, it is possible to wrap the whole extremity with the towel and move passively in ranges desired as the part relaxes. Many persons in applying cryotherapy yield to the temptation merely to wrap a joint, such as the elbow joint, with a cold application. This will not work very well with a two-joint muscle such as the biceps brachii or the biceps femoris. The entire muscle belly must be chilled.

Another effective way of getting good results from the use of cold is to have the patient contract against manual resistance in the direction of the tightness or spasticity of both flexors and extensors. Or one may have the patient contract against manual resistance in the direction of the tightness or spasticity and follow the contraction by voluntary relaxation. This should be done while cold applications are in place. It is possible to wrap the whole extremity with the towel and move passively in ranges desired as the part relaxes. It is essential also that the contraction and the relaxation be done in the range in which the limitation occurs.

Uses of Cryotherapy

Syndromes in which cryotherapy has been especially successful include the following:

Spasticity Disorders. These include, of course, multiple sclerosis as well as cerebrovascular syndromes, postoperative states and certain spinal cord syndromes. Watson[8] noted specific improvement in eight patients with multiple sclerosis who were treated by chilling. The improvements included improved vision and reduction in central scotomas; improvement in gaze paresis; improved swallowing, phonation and articulation; improved willed movement; and improvement in spastic resistance to passive movement of joints. Deep reflexes were increased rather than subdued by cold. Most astonishing was improvement in position sense. All effects were transient.

We have repeatedly observed, in multiple sclerosis patients, augmented strength and endurance from chilling. Conversely we have noted a history of severe increase in symptoms in hot, humid climates, which is almost diagnostic in this disease.

Resistance to passive stretch may melt away under the effects of ice packs but this effect is gone in a few hours or a day. The important point is that persons with craniocerebral injuries or encephalitis who may lie comatose for days or weeks in flexion postures may be preserved from irreversible contracture by brief ice packing and a little stretching just once a day. (We do no stretching in conscious patients.) Obviously if joints and related structures are moved through their entire range even once daily, histological contractures will not have time to occur. But since contracture occurs with stunning suddenness, it is important to start treatment early.

Arthritis and Periarthritis. In dealing with patients with these diseases, selections have to be made. Some patients respond better to heat than to cold. Certain ones respond well to both. In hemiplegic patients, spasticity coexists with periarthritis of the shoulder, as described by Charcot over a hundred years ago. Increased capillary permeability with transudation and swelling of the hand is certainly limited by cold applications, whereas heat tends to increase interstitial edema.

In some instances of acute myalgia of the neck, shoulder or back, we have had good symptomatic relief from cold treatment combined with conventional methods such as traction, massage and relaxation techniques.

General Comment

Other than producing anesthesia of superficial nerves, mechanisms by which the benefits of local applications of cold are brought about are quite unknown. Treatment by local or general chilling has the following advantages:

It is more sedative than heat and at the same time is without its enervating effects.

It is usually more pain-relieving than heat, by the mechanism of transient peripheral nerve block.

It has far more relaxing effect on spasticity and rigidity than heat.

It is, of course, specifically indicated and heat is specifically contraindicated in acute trauma.

While heat has many contraindications cold has only two: cold allergy and Raynaud's disease.

It is without medicolegal risk, whereas burns from hot applications have been the subject of innumerable malpractice suits.

Heat equipment costs vary from modest to highly expensive. Cold is available for the price of ice.

REFERENCES

1. British Medical Bulletin (entire issue): Hypothermia and the effects of cold, 17:1-73, 1961.
2. Brooks, C. M., Koizumi, K., and Malcolm, J. L.: Effects of changes of temperature on reactions of spinal cord, J. Neurophysiol., 18:205-216, 1955.
3. Grant, A. E.: Massage with ice (Cryokinetics) in the treatment of painful conditions of the musculoskeletal system, Arch. Phys. Med., 45:233-238, 1964.
4. Kelly, E., and Fry, W. J.: Isometric twitch tension of frog skeletal muscle as a function of temperature, Science, 128:200-201, 1958.
5. Mead, S., and Knott, M.: Unpublished material.
6. Travell, J., and Rinzler, S. H.: The myofascial genesis of pain, Postgrad. Med., 11:425-434, 1952.
7. Wakim, K. G., Porter, A. N., and Krusen, F. H.: Influence of physical agents and of certain drugs on intra-articular temperature, Arch. Phys. Med., 32:714-721, 1951.
8. Watson, C. W.: Effect of lowering of body temperature on the symptoms and signs of multiple sclerosis, New Engl. J. Med., 261:1253-1259, 1959.
9. Zaimis, E., Cannard, T. H., and Price, H. L.: Effects of lowered muscle temperature upon neuromuscular blockage in man, Science, 128:34-35, 1958.

Primary Lung Cancer

BENJAMIN E. KUCHAR, M.D., *Torrance*

CANCER OF THE LUNG, a rare disease at the turn of the century, is today the most common cause of all cancer deaths in males.[77] It has become one of the most devastating neoplasms known to medical science.

The earliest records of pulmonary carcinoma are found in the writings of Agricola (A.D. 37-93).[69] He and subsequent authors described an unusual disease of the lungs found in men working in the cobalt mines of Schneeberg and Joachimstal. They variously referred to it as tuberculosis, miner's lung and lymphosarcoma of the bronchial glands, but that it was pulmonary carcinoma was not established until Harting and Hesse did so in 1879. As late as 1881, Fraser[24] had to apologize to the Medico-Chirurgical Society of Edinburgh for his inability to present more than a single case in which the disease occurred as a primary affection. The first outstanding American contribution to the subject was a monograph by Adler,[1] 1912, in which he was able to tabulate only 374 cases.

During the succeeding half-century, cancer of the lung has increased in the United States and most other countries at a phenomenal rate. The death rate during the past 30 years, due to bronchogenic carcinoma, has increased 953[3] per cent while the total male cancer death rate in the United States has shown a relatively minor change[19] (see Chart 1). This rise from obscurity to preeminence merits careful consideration.

A considerable amount of investigation has been and is being done in several countries to determine whether this increase is more apparent than real, owing to factors such as aging of the population, improved diagnostic standards and increasing accuracy of death certification.

The possibility of an increasing incidence due to an aging of the population has been eliminated by a number of statistical observations. When the crude mortality rates are corrected to relate to the age-standardized death rates, the factor of aging of the population does not affect the trend.[22] The incidence continues to increase in successively younger age groups.

Some observers have felt that the increasing incidence might be accounted for by better diagnostic standards. However, since the increase is predominantly in the males,[55,71] (Chart 2) one would have to assume a difference in diagnostic acumen according to sex. Also, in view of the prominent increase of the epidermoid over the adenocarcinoma type, one would have to assume a difference in the accuracy of diagnosis according to histological interpretation. Review of more than 40 years' au-

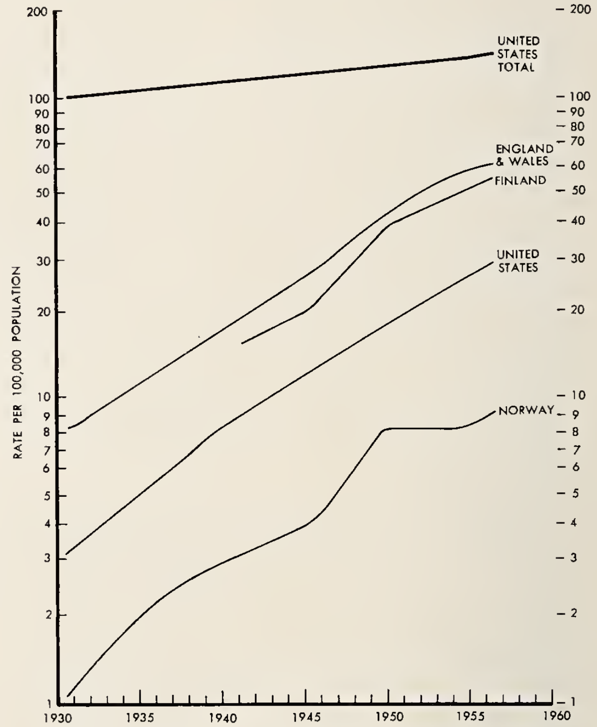


Chart 1.—Incidence of carcinoma of lung in several countries. The heavy line at the top of the chart shows the death rate for cancer of all kinds in males in the United States. Source: Various official government publications.

Submitted 9 November 1965.

Reprint requests to: 2369 Torrance Boulevard, Torrance, California 90501.

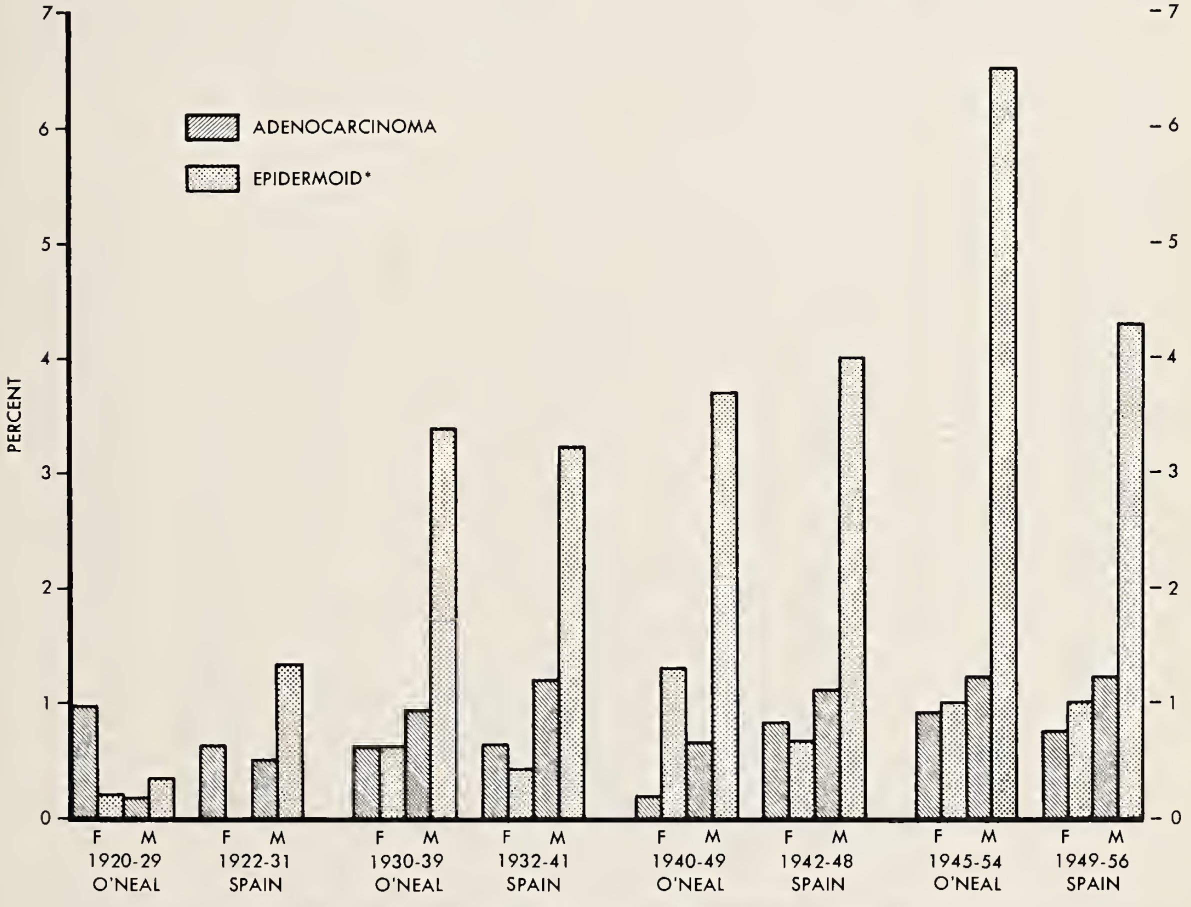
topsy records from a university medical center wherein diagnostic acumen has been high shows a seven-fold increase in the number of cases of primary lung cancer.[55]

Bosner,[10] after investigation of the validity of death certification of cancer of the lung in Leeds, concluded that false positive diagnosis was infrequent and that there was no sex difference in the accuracy of certification. Gilliam[25] pointed out that even assuming some faulty certification of deaths, such errors could not possibly explain the magnitude of the increased incidence of lung cancer.

The sex incidence of primary lung cancer is greater in males than in females. Kirchoff[44] studied a large group of cases from 1900 to 1955. She found the male to female ratio to be approximately 4 to 1 in 1900, and 6 to 1 in 1955. In 1961 Sabour and coworkers,[65] reviewing cases from Cairo and London, arrived at a ratio of 9 to 1. It has been shown that this increasing sex ratio is mainly due to the epidermoid and undifferentiated types, the ratio with regards to adenocarcinoma remaining relatively unchanged throughout the years (Chart 2).

In view of the startling increase in the incidence of lung cancer, many studies have been undertaken in several countries to determine what factors may be responsible for this "pandemic." Since the total death rate from all other cancers in man has not changed appreciably, the investigations have been narrowed down to environmental factors which come in contact with the bronchial epithelium.

Numerous epidemiological studies of air pollution have been carried out.[4,61] There is an increase in the incidence of bronchogenic carcinoma associated with heavy occupational exposures to substances such as dust containing radioactive material, chromates, asbestos, tar and soot and nickel.[40,41,46] The number of workers employed in such occupations is small in proportion to the total population, and, while important in studying the effects of specific etiologic agents, their influence on



*INCLUDES SQUAMOUS, LARGE CELL, SMALL CELL AND UNDIFFERENTIAL CANCERS

Chart 2.—Carcinoma of lung. Relative incidence of epidermoid and adenocarcinoma at various times since 1920, as reported by Spain[71] and O'Neal.[55]

the total incidence of lung cancer is negligible. As will be pointed out later, numerous studies done both in Great Britain and the United States have failed to reveal as strong a correlation with atmospheric pollution as was reported in earlier observations.

A close correlation has been established between the inhalation of cigarette smoke and primary lung cancer. Epidemiological and statistical evidence is based on more than 25 retrospective studies conducted in nine countries as well as three prospective studies carried out in the United States and England.[78] More than 6,000 patients with lung cancer were studied in the retrospective studies alone. Without exception, these studies have revealed a positive relationship between lung cancer and cigarette smoking. A current prospective study of mortality in relation to smoking habits is being conducted in Canada by Best.[7] In a preliminary report he concludes that "epidemiological and statistical studies have shown a definite association between smoking and lung cancer." All studies generally agree that the lung cancer death rate among men with a history of regular smoking for at least 20 years is approximately 10 times greater than that of men who never smoked. Cutler[18] estimated that if 1,000 non-smoking men 40 years of age were followed for 40 years, two would be expected to have carcinoma of the lung by age 60, four by 70, and six by 80 years of age. Among the heavy smokers the estimated incidence would be 23 by 60, 53 by 70 and 80 by 80 years of age (Chart 3).

Kryberg's[48] analysis of 552 cases of lung cancer suggests a classification into two groups according to cell type, Group 1 to include the epidermoid, small cell, anaplastic and undifferentiated carcinomas; Group 2 to include adenocarcinomas, carcinoids and adenomas, mucous gland tumors and bronchioloalveolar cell carcinomas. He found that Group 1 tumors were related to smoking whereas Group 2 tumors were not. These observations are in agreement with those of Auerbach[5] and Doll.[20] Kreyberg[47] checked the validity of his ratio of Group 1 to Group 2 in a study carried out in Finland, a country with an unusually high incidence of lung cancer and low industrial atmospheric contamination, and found a similar linear relationship between Group 1 and the amount of tobacco smoked.

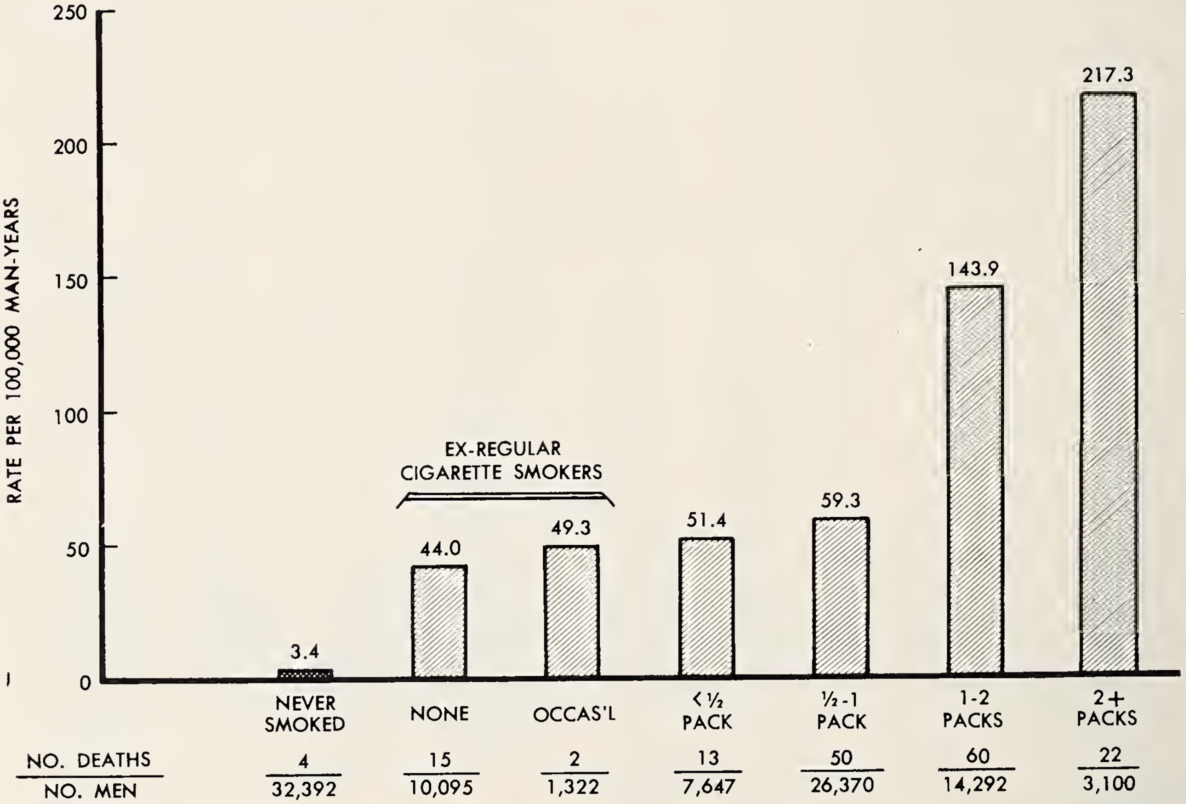


Chart 3.—Carcinoma of lung related to smoking habits (Well established diagnosis, adenocarcinoma excluded). Source: Hammond and Horn.[37]

Doll[21] has shown that a distinct correlation exists between the reported cigarette consumption in 16 countries in 1930 and their lung cancer death rate in 1952. This would indicate that there is a latent period of 20 to 30 years from the beginning of continuous exposure to cigarette smoke to the development of lung cancer. This is in accord with similar studies reported by Clemmeson.[17] Straszewski,[72] conducting a retrospective study in Poland, arrived at the same conclusion. He and his associates suggested that the criterion for classification of smokers should be a factor derived from the intensity times the duration. This aspect of the increasing incidence of lung cancer is extremely important in view of the alarming increase in the number of heavy smoking teenagers seen today.

A remarkably high association between cigarette smoking and death rates for men with lung cancer has been found in rural areas as well as in large cities[37] (Chart 4). In a comparative study of various communities, Haenzel[33] was unable to find any population sub-class that did not have a substantial excess risk among regular cigarette smokers.

The incidence of lung cancer in non-smokers has been studied in relation to industry, occupation and places of residence of large segments of the population.[21] Hammond[38] found that the lung cancer death rates in non-smokers are extremely low irrespective of whether they lived in urban or rural communities, except for those with heavy occupational exposures to carcinogenic substances. Studies of the incidence of lung cancer in Seventh Day Adventists (non-smokers) who live in the smog-ridden Los Angeles basin showed a significantly lower lung cancer death rate than that for the rest of the population in that area.[81] The incidence of respiratory tract cancer in the Seventh Day Adventists was eight times less than the statistically expected number. This was approximately the same as that seen in the female population of Los Angeles. This supports earlier calculations by Wynder[79] and Haenzel[34] that the sex ratio for lung cancer in a non-smoking population would tend to be unity.

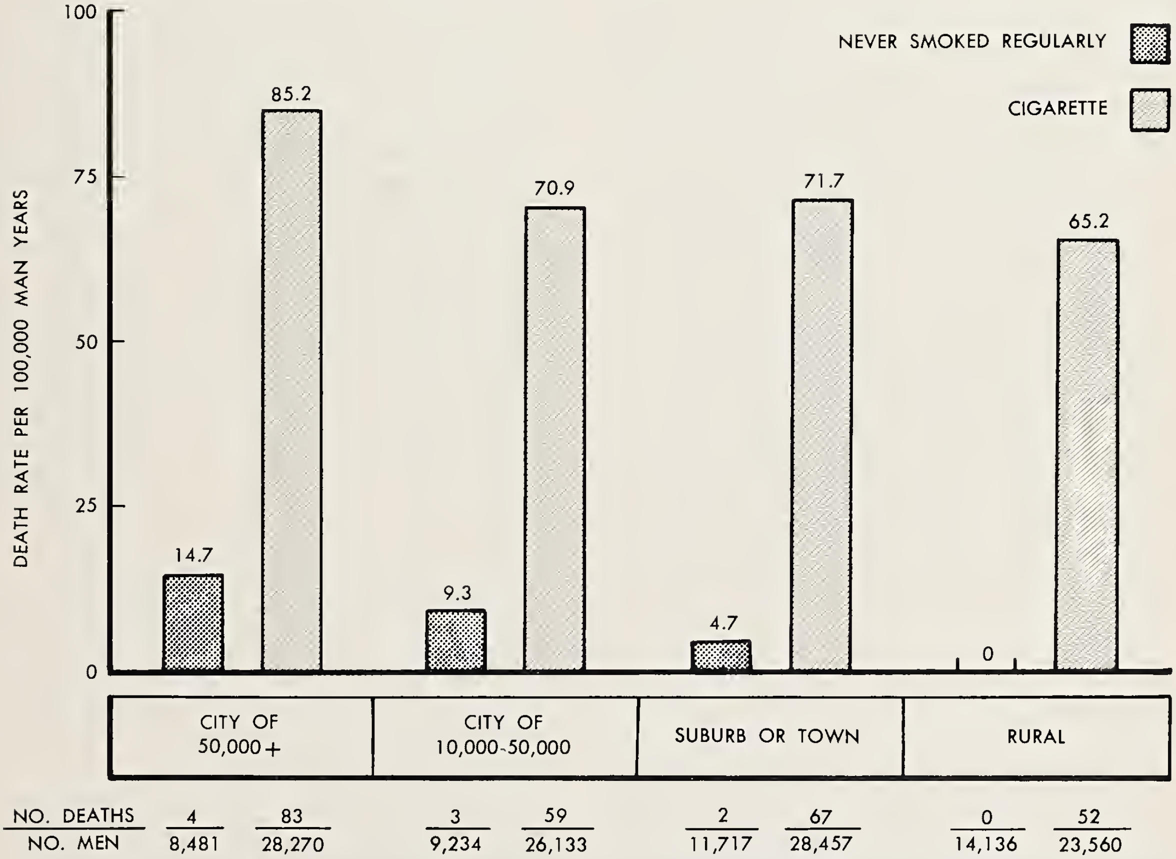


Chart 4.—Carcinoma of lung in smokers and non-smokers, urban, suburban and rural (Well established diagnosis, adenocarcinoma excluded). Source: Hammond and Horn.[37]

Hammond and Garfinkel,[36] in a study of smoking habits of men and women, found that the proportion of regular cigarette smokers is much smaller in women than in men. Also the average female smoker was found to start later in life and smoke for fewer years. They were also found to inhale much less than men. It was concluded that the proportion of heavy habitual smokers is much smaller among women than men.

Regarding the incidence of lung cancer in relation to type of smoking, it has been found in at least two studies[11,37] that lung cancer is less likely in cigar smokers than in cigarette smokers, and that pipe smokers are almost but not quite on the same level as non-smokers.

We are frequently asked how much good it does to quit after one has been smoking for "years." Best,[7] in his Canadian series, and Hammond and Horn[37] in the United States series concluded that cutting down from a high to a low amount of cigarette smoking or discontinuing the habit completely resulted in a reduced death rate.

Considerable progress has been made in the laboratory during the past 10 years in confirming an association between the development of lung cancer and chemical substances found in cigarette smoke.[8,80] Rocky[64] recently reported the production of bronchogenic carcinoma in dogs (in which primary lung cancer is otherwise unknown) by repeated application of cigarette smoke residue to their bronchial mucosa. Microscopically all of the histological changes seen in the development of bronchogenic epidermoid carcinoma were seen in these dogs. Cancer did not develop in any of the control series. Nickel carbonyl has been found to have a carcinogenic effect on the bronchial mucosa. This has repeatedly produced pulmonary cancer in rats. It has been found that cigarettes contain from 1.59 to 3.07 micrograms of nickel per cigarette. A person inhaling mainstream smoke from two packages of cigarettes per day would in one year inhale 5,400 micrograms of nickel or three times the amount observed to be carcinogenic in rats.[73]

Undoubtedly there are other factors involved in the etiology of cancer of the lung, such as chronic infection and scar tissue.[76,82] It is also generally agreed that there exists an individual susceptibility and resistance to this disease. As with any other cancer, the complete etiologic delineation has not yet been determined. However, in view of the mass of presumptive, epidemiological, statistical, pathological and experimental evidence which has been and is accumulating, one cannot but conclude that there is a definite relationship between cigarette smoking and lung cancer. This was the conclusion of the British Medical Research Council,[29] the World Health Organization[77] and the Report of the Advisory Committee to the Surgeon General of the Public Health Service, after an exhaustive review of the accumulated evidence to date.

Pathology

Primary cancer of the lung may be classified as follows:

I. Bronchogenic Carcinoma
    A. Epidermoid carcinomas.
    B. Small cell anaplastic carcinomas (oat cell).
    C. Undifferentiated carcinomas.
    D. Adenocarcinomas.

II. Adenomas
    A. Carcinoids.
    B. Mucous gland tumors, mainly cylindromas.

III. Bronchiolo-alveolar carcinomas.

Approximately 60 per cent of the bronchogenic carcinomas are of the epidermoid type, 25 to 30 per cent are small cell and undifferentiated and 8 to 10 per cent are adenocarcinomas. Listed according to frequency of occurrence, the adenomas, bronchiolo-alveolar carcinomas and mucous gland tumors together represent about 5 per cent of the total. Approximately 75 per cent of the bronchogenic carcinomas arise in the major bronchi and 25 per cent in the peripheral bronchial system. It is generally agreed that over 50 per cent of these primary tumors arise in the upper lobes (slightly more on the right), whereas only 5 per cent arise in the middle lobe. The epidermoid, small cell and undifferentiated types are seen more frequently in the bronchi of men exposed to high concentrations of carcinogenic substances, whereas adenocarcinomas are found in non-smokers and women and do not seem to be related to substances recognized as carcinogens. The tremendous increase in the incidence of lung cancer has been associated with the epidermoid, small cell and undifferentiated groups. These in turn have been found almost exclusively in heavy cigarette smokers.

It has been found that the changes most characteristic in mucosa exposed to irritation by carcinogenic substances are basal cell hyperplasia, squamous metaplasia and carcinoma in situ.[5,14]

Auerbach,[5] making three separate studies of autopsy material over a period of five years, found that people dying of bronchogenic carcinoma showed all types up to and including frank invasive carcinoma. In all three studies, the least changes were found in subjects who did not smoke or smoked only occasionally. He did not find a single case of carcinoma in situ in a non-smoker.

Metastatic spread of these lesions is usually early and extensive because of the copious lymphatic drainage and the enormous volume of blood circulating through the lungs to all other parts of the body. Burford[13] reported that examination of the resected specimens of five-year survivors revealed 45 per cent with lymph node involvement and 8 per cent with blood vessel invasion. Pryce[62] examined 183 resected carcinomas and found artery and vein invasion in over 40 per cent. The most common sites of lesions metastatic from these tumors are the local and regional lymph nodes, the brain, liver, bones and adrenal glands. Halpert[35] reported that 26 per cent to 38 per cent of metastasis is to the brain. It is difficult to predict when metastasis from a bronchogenic carcinoma will occur. According to Goldman[26] the extremely well differentiated epidermoid carcinomas may remain localized for long periods, and metastasis then occur only to regional lymph nodes. Burford[13] found that 75 per cent of the resected specimens of five-year survivors were of the epidermoid type. The size of the primary lesion may not be related to its propensity to metastasis. There are cases in which the patient dies of distant metastasis, the primary pulmonary lesion being so small that diagnosis is not established until postmortem examination. Generally speaking, however, the longer one procrastinates and the larger the lung cancer becomes, the higher will be the incidence of distant metastasis with the resulting grim prognosis.

Bronchial adenomas are relatively infrequent tumors, making up less than 5 per cent of all neoplasms of the bronchi.[52] They are found with about equal frequency in males and females and are generally seen in patients of a younger age group, the average age for males being 42 and for females 38 years. They do not seem to be related to air pollution or smoking. These tumors arise predominantly in the main stem bronchi, although a few may arise in the secondary and the tertiary bronchial divisions. Endobronchial biopsy is positive in over 75 per cent of the cases. They are usually slow-growing and are quite vascular, accounting for one of the most frequent presenting symptoms, recurrent hemoptysis over a period of months or even years. Many clinicians tend to assume that tumors of this group, because of their classification as adenomas, remain localized within the bronchial lumen in which they arise. Graham[27] was the first to stress that these tumors were not entirely benign and that local invasion, lymphatic spread and, rarely, distant metastasis did occur. McBurney[49] expressed belief metastasis occurs from about 10 per cent of bronchial adenomas. It is because of this that many pathologists prefer to classify these tumors as Grade I carcinomas. The overall prognosis, however, is good, being better than 80 per cent five-year survival.

The cylindromatous type of bronchial adenomas represent approximately 5 to 10 per cent of this group.[50] They are more prone to metastasis and are important because prognosis is considerably poorer than for the true bronchial adenomas.

Bronchiolo-alveolar carcinomas make up a small proportion of primary lung cancers, 1.5 per cent. When solitary, they are usually associated with varying degrees of fibrosis and chronic inflammation, and it is because of this that they are frequently first diagnosed as segmental pneumonitis or as "chronic lung scar." This lesion grows slowly and metastasis is a late occurrence. The cure rate may be as high as 80 per cent when the lesion is surgically removed before lymph node extension has occurred.

Clinical Features

The clinical evolution of lung cancer may be more insidious than that of any other neoplasm. In 1892, Sir William Osler[56] commented, "The patient may, indeed, as noted by Walshe,[75] present no symptoms pointing to intrathoracic disease." The first symptoms to appear may be so mild that they are overlooked by the patient and his physician for weeks or even months. They are dependent upon the size, location and pathologic character of the tumor. Those of relatively small size located in the larger bronchi and those in the more peripheral pulmonary parenchyma may remain silent for weeks, months, or even years. In contrast, those obstructing the smaller bronchi or ulcerating early may produce signs and symptoms which could lead to early detection and treatment if the symptoms were acknowledged by the patient and intelligently pursued by the physician. In a retro-

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE

spective study of proved lung cancer cases, The Philadelphia Neoplastic Research Project found 38 out of 40 cases in which some symptoms were present before there were demonstrable roentgenographic changes.[11]

Cough is one of the earliest and the most frequent symptoms of lung cancer. It is present in approximately 80 per cent of cases. However, because this symptom is associated with so many non-neoplastic conditions such as upper respiratory infections, chronic bronchitis, "smoker's cough," bronchiectasis and various allergic reactions, it is frequently ignored or treated symptomatically until more alarming symptoms develop. It must be borne in mind that cough is a reflex mechanism of the respiratory system produced by irritation of the bronchial tree. A person who does not have a chronic cough generally will seek medical attention much sooner when this symptom appears than a chronic cougher who has a change in the cough he has had for years. Yet it is the heavy smoking chronic coughing male in the fourth, fifth and sixth decades of life who has the highest risk of lung cancer. He should be classified as being in a special "high risk group" and screened at regular intervals with complete radiological and cytological studies. The cough caused by bronchogenic carcinoma usually begins as nonproductive and hacking. As it progresses, clear mucoid and then varying degrees of thick purulent sputum may be produced, depending upon the amount of secondary infection present.

Wheeze is a presenting symptom in only about 20 per cent of the patients with bronchogenic carcinoma. The presence of a wheeze may be detected by someone other than the patient, while he is sleeping in a certain position. Others may notice it only during paroxysmal coughing. Since patients with a chronic productive cough may take a wheeze for granted, they should be warned that when a wheeze cannot be "coughed out" the need for expert evaluation is in order. In any case in which "asthma" rather suddenly develops, whether bilateral or unilateral, careful investigation is warranted.

Hemoptysis is a symptom which usually arouses enough anxiety in a patient to induce him to seek medical care promptly. There are, however, still persons who will conceal this symptom, fearing that it might mean loss of a job or confinement in a sanatorium. Fortunately, with improved health education and the decreasing incidence of tuberculosis, fear of this sort is rapidly disappearing. The three most common causes of hemoptysis are bronchiectasis, tumor and tuberculosis, in that order of frequency of occurrence. Approximately 40 per cent of the bronchogenic carcinomas and 80 per cent of the bronchial adenomas will produce this symptom. The physician should carefully explain to the patient the urgent need for a complete, well organized investigation to establish the exact cause of the bleeding or to at least rule out the presence of tumor. It is important to emphasize that even if a patient has bronchiectasis or tuberculosis, the coexistence of a tumor must still be ruled out. There will be a small proportion of patients in whom all the tests including roentgenographic, bronchoscopic, bronchographic, cytologic and dermatologic will be negative. It is important to follow these patients carefully with periodic examinations to rule out the presence of a tumor which may have been too small to be detected by any of these means at the time of the initial episode of hemoptysis.

Recurrent fever with nonresolving persistent or recurrent pneumonitis, especially in an upper lobe, should be regarded with strong suspicion. This is particularly important in heavy smoking males over the age of 40. Frequently symptoms of general malaise, nocturnal diaphoresis, anorexia, and loss of weight will cause the patient to consult his physician. Physical examination and radiographs will establish the diagnosis of pneumonia, and he may be placed on a therapeutic medical regimen. Decided subjective improvement may occur within a few days, but the patient should never be discharged without follow-up physical examination and repeat of x-ray films of the chest. These studies may reveal only partial resolution of the infiltration, in which case further diagnostic as well as therapeutic measures should be pursued. The physician should not be lulled into a sense of security by initial improvement. If a residual density persist after three to six weeks of a well organized medical regimen, the patient should be given the benefit of a complete examination for thoracic disease, consisting of special x-ray studies including bronchography, bronchoscopy, skin tests and bacteriological and histological studies of the bronchial secretions. An early bronchogenic carcinoma no larger than a few millimeters in diameter may cause atelectasis and pneumonitis of a pulmonary segment large enough to be easily demonstrated by a good x-ray film. If the tumor is diagnosed and surgically removed at that stage, the patient is given a better than 50 per cent chance of cure whereas only a few weeks or months of unwarranted procrastination will reduce the chance of cure to 8 per cent or less.

Dyspnea may be due to any one of a number of diseases which in turn could be caused by an early bronchogenic carcinoma. Spontaneous pneumothorax may be produced by rupture of a bleb produced by emphysematous changes in a lobe or segment resulting from the ball-valve action of a small intrabronchial tumor. Segmental atelectasis with segmental or lobar pneumonitis caused by an early tumor may produce rather pronounced dyspnea in a patient whose pulmonary reserve is compromised by preexisting pulmonary emphysema, fibrosis or bronchiectasis. Dyspnea resulting from pleural effusion may be due to the peripheral pneumonitis and atelectasis caused by a relatively small intrabronchial tumor and may carry a fairly good prognosis, in contrast to the effusion caused by extensive lymphatic and pleural involvement, which invariably carries a grim prognosis. Here again the importance of a complete chest evaluation and a rigid follow-up program is emphatically stressed.

Pain, unfortunately, is usually one of the later manifestations of bronchogenic carcinoma. Yet it is often the symptom which finally induces the patient to seek medical attention. An individual may tolerate a cough or wheeze or recurrent fever with anorexia and weight loss for weeks or months while he tries various home remedies. Unfortunately he may not consult a physician until pain forces him to do so. The pain may be caused by a pleuritis secondary to segmental or lobar pneumonitis with a relatively small tumor, but too often it represents spread of the tumor to involve pleura, nerves, diaphragm or the skeletal system.

The symptoms and signs caused by distant metastasis of lung cancer are important in that they may be the first manifestations of this disease. Headache, visual changes and changes of equilibrium with Jacksonian convulsions may be due to cerebral metastasis. Hoarseness may be due to recurrent laryngeal nerve involvement. Horner's syndrome (myosis, ptosis and enophthalmos) may represent involvement of the cervical sympathetic ganglia. Persistent arm, neck and shoulder pain may result from involvement of the brachial plexus. Back and chest pain may be due to skeletal metastasis or direct extension of the tumor to the vertebrae or ribs. Dysphagia may be caused by either direct invasion or compression of the esophagus by the bronchogenic carcinoma. Anorexia, many times of a capricious type, may indicate liver metastasis. Edema and cyanosis of the face, neck and upper extremities, with increased pressure in the veins of the neck and arms, is evidence of some compression of the superior vena cava and may represent extensive involvement of the right superior mediastinum. The carcinoid syndrome may be seen with metastatic bronchial adenomas and has been reported rarely in the presence of oat cell carcinomas. Gynecomastia is on rare occasion one of the early symptoms of lung cancer. Hypertrophic pulmonary osteoarthropathy may be associated with bronchogenic carcinoma and has been observed to regress after removal of the primary tumor.[59]

Diagnosis

Early diagnosis of bronchogenic carcinoma is at present one of the most important factors influencing the ultimate prognosis. A constant awareness of the disease with a high index of suspicion on the part of the attending physician is mandatory. The patient should be made aware, through careful discussion and presentation of the facts about lung cancer, of the extreme importance of periodic x-ray and physical examinations of the chest with appropriate follow-up studies of any positive findings. This is especially true for those patients classified in the "high risk" group.

The patient's history should always include a complete review of the respiratory system even though the presenting complaint may be a seemingly unrelated medical, obstetrical or surgical problem. Past and present exposures to the various types of industrial and atmospheric pollutions should be recorded. A history of the patient's smoking habits with reference to duration, intensity and type is of paramount importance. These data along with the patient's age and sex can serve as a baseline in estimating his statistical risk of lung cancer. An accurate record of previous infections, injuries and thoracic roentgenograms may prove of infinite value in the appraisal of subsequent abnormal physical or radiological findings. Nothing can be as valuable to a radiologist or a chest specialist, with the responsibility of interpreting an x-ray density, as a set of previous films for comparison. It is surprising how often patients will have forgotten about previous x-ray examinations until specifically questioned about them. Any change in the cough habits of a patient should be included in a good history with special reference to causative factors, periodicity, influence of positional changes, character (dry or productive) and, if productive, the amount, consistency, color and odor of the sputum. In addition it is imperative to make specific queries regarding hemoptysis, wheeze, chest pain, dyspnea, hoarseness and dysphagia.

Radiographic studies are one of the most important means available for early detection of lung cancer. The use of the Mobile Unit Chest Survey film has in general been disappointing from the standpoint of early detection of pulmonary carcinoma.[69] One of the reasons for this is that a large proportion of the persons examined are women and children, with relatively few men over the age of 40 included.[31] The creation of a false sense of security is probably the outstanding hazard of the usual survey minifilm. A reluctance on the part of an asymptomatic patient to follow through on a suspicious survey finding accounts for a considerable number of failures in surveys of this type.[32] This fact again emphasizes the importance of public education and of closer physician-patient relationship. The lesion when at an early enough stage to give a relatively good chance for cure may be completely missed on the single view minifilm, whereas lesions large enough to be detected by this examination are often already far advanced. It has been estimated that approximately 8 per cent of the bronchogenic carcinomas are detected by survey, yet the prognosis may be poorer than for the total number of treated bronchogenic carcinomas.[30,60]

Fluoroscopic examination as a routine screening diagnostic procedure is unsatisfactory and is mentioned only to be condemned.

It is imperative that at least two views always be taken for an initial diagnostic roentgenogram. Often lesions or areas of segmental atelectasis that cannot be seen on the usual posteroanterior film may be clearly visualized on a lateral film. The only possible justification for taking a single view would be for follow-up studies of a previously diagnosed and localized density.

The importance of giving the radiologist more than just a simple written request for an x-ray examination cannot be overemphasized. When the radiologist knows what is suspected and has a brief resumé of the history and positive findings, he may be able to suggest further x-ray studies at the time of the initial x-ray examination and thereby save considerable time in the ultimate diagnosis and subsequent treatment.

Skin tests are important adjuncts in the evaluation of a potential lung carcinoma. The tuberculin and coccidioidin tests are the two usually used, the latter being quite important in the Southwestern states because of the presence of coccidiomycosis. This disease can mimic many pulmonary diseases, including bronchogenic carcinoma. A negative reaction to skin test can be quite significant, but a positive reaction certainly does not rule out carcinoma. It must be kept in mind that this is but a small part of the entire clinical complex, and one should not be given a sense of security by a positive or negative reaction. It is possible for bronchogenic carcinoma to coexist with either active pulmonary tuberculosis or coccidiomycosis.

Bronchoscopy is an essential examination in any patient suspected of having a bronchogenic carcinoma, for approximately 75 per cent of these tumors are found in the major bronchi. The incidence of positive histologic diagnosis by bronchial biopsy ranges from 30 per cent to 50 per cent. In the hands of a skilled endoscopist the procedure can be carried out with little discomfort. It is emphasized that the technical skill alone does not identify a good diagnostic endoscopist. It is mandatory that he possess an intimate anatomic physiologic and pathologic knowledge of the lungs and bronchi. Any patient who is a candidate for pulmonary resection should have bronchoscopic examination, preferably by the thoracic surgeon who is to do the thoracotomy. By direct visualization he can determine the general condition of the major bronchi and the gross intrabronchial extension of the tumor. Involvement of the main carina or both main stem bronchi may indicate inoperability in what would have appeared to be an operable tumor by other criteria, thus saving the patient unnecessary thoracotomy. The surgeon is also given a clue as to the feasibility of lobectomy if, at the time of thoracotomy, that procedure should be indicated. In the patient who has bronchoscopic examination without x-ray evidence of tumor, an early intrabronchial carcinoma may be found, giving a chance for early resection and a good prognosis. Generally speaking, however, a positive diagnosis on bronchoscopic visualization may predict a lower resectability rate by 30 to 50 per cent. Even when the conditions observed at bronchoscopic examination are grossly normal, secretions may be collected for histological and bacteriological studies.

The cytologic examination of sputum and bronchial washings has proved to be a valuable adjunct in the diagnosis of bronchogenic carcinoma when done by experienced cytologists equipped with special laboratory facilities and trained personnel. Ackerman[2] pointed out that a false-positive diagnosis can be rendered in patients with atypical pneumonia, pulmonary infarction, lipid pneumonia, mycotic disease or tuberculosis. Green and Umiker[15] expressed belief that chronic bronchitis due to heavy smoking may lead to false-positive diagnosis and Koss[45] emphasizes that cellular changes produced by irradiation may be extremely difficult to differentiate from those of cancer. It must be remembered cytologic examination usually is negative in the presence of peripheral bronchogenic carcinomas. Accordingly, Overholt[57] reported that false-negative cytologic diagnosis occurred in approximately 25 per cent of proved cases of lung cancer in his clinic.

It is emphasized that negative reports do not always mean that a cancer is not present. When a clinician has strong radiographic and clinical evidence of lung cancer, multiple negative cytologic examinations should not influence him, especially if operation is otherwise feasible. When clinical evaluation does not give the impression of lung cancer but cytologic examination of the sputum is positive for malignant cells, a careful correlative clinical and cytologic reevaluation is necessary. It must be remembered that although cytologic examination by trained personnel is a valuable laboratory aid in the diagnosis of lung cancer, it represents but a small part of the diagnostic array. There is still no substitute for careful evaluation, correlation and clinical judgment.

Scalene node biopsy has been found useful in determining metastatic spread to regional lymph nodes. It may account for 15 to 20 per cent of the positive diagnoses. The biopsy should be done even though there are no grossly palpable lymph nodes.[39] The presence of positive lymph nodes generally places the patient in the inoperable group, with radiation or chemotherapy or both being offered as palliative measures. However, with the encouraging results recently reported with preoperative irradiation followed in four to six weeks by surgical resection, a new field of therapy has been opened which may have more to offer to these patients than either means alone.

Treatment

In discussing the treatment of lung cancer, Walshe,[75] in 1854 stated, "Cancer seated in the lungs is even less under the control of remedies than when occupying some other localities . . . symptoms must be relieved as they occur, by ordinary measures." Salter,[66] in 1869, regarding the treatment of lung cancer was said to ". . . doubt if we can in such a case put off the final catastrophe for a single hour."

From these gallant yet grim days until but 30 years ago, the ultimate outlook for the patient with this disease remained the same. With the successful surgical extirpation of a bronchogenic carcinoma by Evarts Graham in 1933,[28] a new era in the management of lung cancer began. Since that date thousands of years of human lives have been saved and countless others have been usefully prolonged by effective palliation. Yet it is an alarming fact that there are members of our profession who still cling to the attitude that existed in the middle of the 19th Century. If the defeatist derives his attitude from ignorance he should be educated.

Surgical operation offers the best hope for cure in bronchogenic carcinoma. Of the total number of cases of lung cancer seen, approximately 70 per cent are considered operable. Operability refers to whether or not the patient is a candidate for exploratory thoracotomy; it does not imply resectability. The incidence of operability varies considerably from one clinic to another as well as in different parts of the world. Some clinics have maintained approximately the same rate during the past 25 years, but generally speaking there has been a gradual increase from as low as 30 to 40 per cent to the present figure of 70 per cent. It is hoped that with diligent education of the public, with special emphasis on the "high risk" groups, the operability rate will continue to increase.

In each patient, operability is determined by a number of findings at the time of physical examination. Inoperability is generally considered absolute when any one of the following is present:

- Distant metastasis to the brain, liver or skeletal system.
- Terminal disease with little chance to survive any surgical procedure.
- The presence of bilateral pulmonary cancer as seen radiographically or bronchoscopically.

- Direct invasion of the mediastinum with involvement of such structures as the esophagus, myocardium or trachea.
- Bloody pleural effusion containing absolute cytologic evidence of pleural invasion. A simple effusion, even if bloody, may be due to local pleural involvement by infection distal to the tumor or to peripheral infarction of the lung itself. Hydrothorax or hemothorax of this type certainly should not in itself contraindicate exploratory thoracotomy.

Findings which once were considered to be an indication of absolute inoperability but are now becoming relative are:

- The presence of neoplastic mediastinal lymphadenopathy. Overholt[57] found that 20 per cent of his patients with five-year survival had had positive mediastinal nodes. None of these patients had had preoperative scalene node biopsy or exploratory superior mediastinotomy. He pointed out that undoubtedly some of that 20 per cent group would have had positive biopsy and therefore would have been rejected for intrathoracic exploration. The use of preoperative irradiation followed by resection has improved operability in such cases as well as in cases of superior sulcus tumors with brachial plexus and bone involvement.[67] The superior vena cava syndrome is no longer an absolute contraindication when this therapeutic regimen is utilized.
- Clinical evidence of selective involvement of the recurrent laryngeal or phrenic nerve. Although involvement of these structures usually indicates extensive mediastinal invasion, if there is no corroborative radiographic, bronchoscopic or clinical evidence of mediastinal involvement, one should consider the possibility of a fortuitous local extension which might well be within the limits of respectability.
- The patient who appears inoperable because of general debility may be so restored by the judicious use of antibiotics, vigorous bronchial toilet and well planned and administered supportive measures, that in the absence of absolute contraindications, exploration and resection could be accomplished. It should be kept in mind that occasionally major signs and symptoms may be produced by a small lung cancer. It is imperative that careful clinical evaluation be carried out in each individual case.

The resectability of bronchogenic carcinoma varies in different clinics. However, it seems to averages 35 to 40 per cent of the total cases of lung cancer, or 70 to 80 per cent of the cases in which operation is done. Churchill reported that in a 10-year cumulative study at Massachusetts General Hospital the resectability rate increased from 25 per cent in the period 1933-1948 to 35 per cent from 1948 to 1956.[16] In determining resectability, most surgeons feel that all cancer-bearing lung tissue and tumor mass should be removed unless extensive mediastinal invasion creates insurmountable technical problems.

The problem of how much lung to remove has received increasing attention during the past 10 years. Ochsner expressed the opinion that pneumonectomy is the treatment of choice when possible.[54] Other observers, however, have shown that the survival rates for lobectomy are as good or in some cases even better than those for pneumonectomy.[6,15,16,57] In addition, the patients have much less pulmonary disability when only a lobe is removed, thus extending the chance for curative resection to those patients for whom operation might have been considered infeasible because of borderline pulmonary reserve. The operative mortality for pneumonectomy is almost twice as great as for lobectomy, 10 to 20 per cent against 5 to 10 per cent.[15,16,57,63] The morbidity, especially for right pneumonectomy, is considerably greater than for lobectomy. An important point regarding the mortality of pulmonary resection is brought out by Reid. In the cases he reported, in Scotland, the mortality was 23 per cent for pneumonectomy and 13 per cent for lobectomy. He believed that this higher mortality rate than that reported in other countries was due to the unusually high incidence of chronic bronchitis, bronchiectasis and pulmonary emphysema in Scotland.

This important point should be taken into consideration when preparing a patient for pulmonary operation: Since 95 per cent of the patients with lung cancer are heavy smokers with chronic bronchitis, excessive bronchial secretions and obstructive pulmonary emphysema, a strict medical regimen two weeks before operation will appreciably reduce the incidence of operative and postoperative complications. This should include discontinuance of smoking, the use of expectorants, bronchodilators, postural drainage and, when indicated, specific antibiotic therapy. Postoperatively the patient must not be incapacitated by the injudicious use of narcotics and sedatives. Hourly turning, induction of coughing and, when necessary, intrabronchial suctioning by a diligent, expertly trained special nurse during the first postoperative 24 to 48 hours, can be even more important than the surgical procedure itself in determining the ultimate surgical mortality and morbidity.

Radiation therapy with Cobalt-60 and two-million volt x-ray has received increasing attention during the past decade. Generally speaking, the results with this modality alone have been disappointing, although Smart[70] reported a survival rate in selected cases of bronchogenic carcinoma comparable to that for patients treated surgically.[70] Other studies, however, have not agreed with these findings.[12,43,53] It is generally agreed that radiation therapy has a definite place in the palliation of inoperable and unresectable lung cancer. It has been of considerable value for the relief of pain and the management of the sequelae of inoperable bronchial obstruction.

The use of subtherapeutic doses of radiation followed in four to six weeks by surgical resection has, to date, offered encouraging results.[9,58,67] Five-year statistics are awaited with great hope.

Chemotherapy alone has been of no value as a curative agent in the management of lung cancer.[42]

Prognosis

The overall five-year survival rate for bronchogenic carcinoma is at present 8 per cent. Mersheimer, reporting in 1960 on the figures of the *Cancer End Results Evaluation Program,* showed that the five-year survival rate for males in whom the disease was diagnosed before 1950 was 3 per cent as compared with 5 per cent for those after 1950.[51] In cases in which the tumors were classified as localized, the survival rate was better—9 per cent if the diagnosis was before 1950 and 17 per cent if after 1950.

In patients receiving surgical therapy, the five-year survival rate for those with localized tumors is 40 to 50 per cent. When the tumor has invaded the regional lymphatics it drops to 15 to 20 per cent (Chart 5).

Studies of surgically treated bronchogenic carcinoma show a low survival rate during the first 30 months, but 75 per cent of the patients who live 30 months will be alive after five years[16,43,57,63] (Chart 5). It has been found that most of these early deaths are due to distant metastasis, and it is felt that in such cases metastasis either has already occurred or is produced at the time of operation. It will be interesting to see if preoperative irradiation will improve the five-year survival by reducing the number of cases in which distant metastasis is brought about by surgical manipulation of the tumor at the time of resection.

It has been shown that the five-year survival rate for "coin lesions" that turn out to be primary lung cancer is approximately 60 per cent. Overholt reported that carcinoma was found in 40 of 100 cases in which thoracotomy was done for coin lesions. The operative risk during this asymptomatic period is 2 per cent or less. When this risk is compared with the mortality, morbidity and survival rate associated with advanced bronchogenic carcinoma, there seems no question as to the preferred management of a pulmonary density the exact cause of which cannot be determined.

Summary

In summary, we find ourselves involved in a desperate struggle with a disease which continues to increase and to take a high death toll in spite of advancing medical science. Nonetheless, over the years there has been a slow but definite advance by medicine as seen in higher operability and survival rates and lower surgical morbidity and mortality.

The causative factors have been and are being actively investigated by medical scientists, epidemiologists and statisticians throughout the world. Their findings indicate beyond reasonable doubt that there is a direct causal relationship between cigarette smoking and lung cancer. These postulates have been satisfied:

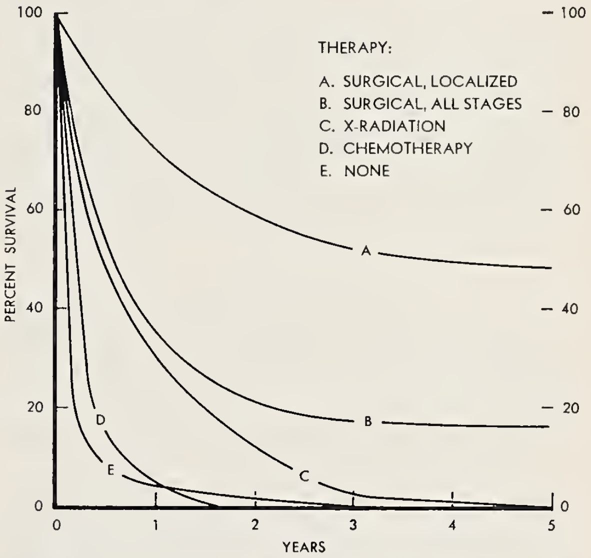


Chart 5.—Carcinoma of lung. Survival by type of therapy.

- Statistical evidence has been presented to show that cancer of the lung exists as an ever increasing threat to the population.

- Epidemiological evidence has demonstrated a direct association between lung cancer and cigarette smoking.

- Lung cancer can be produced in experimental animals by use of carcinogenic extracts from cigarette smoke.

- It has been shown that in the absence of cigarette smoking, all other factors remaining unchanged, the incidence of lung cancer is reduced.

The fact that lung cancer will develop in some 30,000 Americans this year warrants deep concern. In face of the overwhelming evidence presented throughout the world, one cannot be influenced by the tobacco industry's "The cause of cancer is not known." Many diseases such as cholera, puerperal sepsis, smallpox and scurvy, to name but a few, were being controlled long before their exact causes were known. When carcinogenic agents are found in industrial operations, elaborate detection systems are devised and stringent regulations enforced to protect the workers. The time has come for the tobacco industry to admit the existence of this public health hazard and to take steps to eliminate it. We as physicians have a moral obligation through education to curb the irresponsible advertising of the tobacco industry which encourages teenagers to start using tobacco before they are old enough to clearly evaluate the facts of the situation.

The only hope for the 30,000 Americans a year who have cancer of the lung will be in early detection and prompt, concise treatment, with a never ending endeavor to reduce the procrastination factor. This can be accomplished only through diligent education of the public and an alert, intellectually honest positive attitude on the part of the physician.

REFERENCES

1. Adler, I.: Primary Malignant Growths of the Lungs and Bronchi, Longmans Green & Co., New York, 1912.

2. Akerman, L. V., and Spjut, H. J.: Exfolliative cytology and pulmonary cancer, Acta Unio Internat. Contra Cancrum, 16:371-376, 1960.

3. American Cancer Society, Inc.: Is Smoking Worth It, educational motion picture, 1962.

4. Anderson, J. R.: Epidemiologic studies of air pollution, Diseases of the Chest, 42:474-481, 1962.

5. Auerbach, O., Stout, A. P.: The role of carcinogens, especially those of cigarette smoke, in the production of precancerous lesions, Proc. Fourth National Cancer Conf., J. B. Lippincott Co., Philadelphia, 297-304, 1960.

6. Belcher, J. R.: Lobectomy for bronchial carcinoma, Lancet, 2:639-642, 1959.

7. Best, E. W. R., Josie, G. H., Walker, C. B.: A Canadian study of mortality in relation to smoking habits —a preliminary report, Canadian J. of Public Health, 52:99-106, 1961.

8. Blacklock, J. W. S.: Production of lung tumors in rats by 3:4 benzpyrene, methylcholanthrene and condensate from cigarette smoke, Brit. J. Cancer, 11:181-191, 1957.

9. Bloedorn, F. G., Cowley, R. A., Irradiation and surgery in treatment of bronchogenic carcinoma, Surg., Gynec. & Obstet., 111:141-146, 1960.

10. Bosner, G. M., and Thomas, G. M.: An investigation of the validity of death certification of cancer of the lung in Leeds, Brit. J. Cancer, 13:1-12, 1959.

11. Boucot, K. R.: The Early Detection of Bronchogenic Cancer, Proc. Fourth National Cancer Conf., J. B. Lippincott Co., p. 324, Philadelphia, 1960.

12. Boyd, David P., Souders, C. R., Smedal, M. I., O'Hallaren, J. D., Trump, J. G.: Surgery and supervoltage therapy in treatment of carcinoma of the lung, J.A.M.A., 179:253-256, 1962.

13. Burford, H., Ferguson, T. B., Spjut, H. J.: Results in the treatment of bronchogenic carcinoma: Analysis of 1,008 cases, J. Thor. Surg., 36:316-328, 1958.

14. Carroll, R.: Changes in the bronchial epithelium in primary lung cancer, Brit. J. Cancer, 15:215-219, 1961.

15. Christiansen, K. H., Smith, D. E.: Bronchogenic carcinoma: A sixteen-year study, J. Thor. & Cardiovas. Surg., 43:267-275, 1962.

16. Churchill, E. D., Sweet, R. H., Scannell, J. G., Wilkins, E. W., Jr.: Further studies in surgical management of carcinoma of lung: Further study of cases treated at Massachusetts General Hospital from 1950 to 1957, J. Thoracic Surg., 36:301-308, 1958.

17. Clemmesen, J., and Nielsen, A.: The geographical and racial distribution of cancer of the lung, Schweiz. Ztschr. allg. Path., 18:803-819, 1955.

18. Cutler, S. J., and Loveland, D. B.: The risk of developing lung cancer and its relationship to smoking, J. Nat. Cancer Inst., 15:201-211, 1954.

19. Davies, D. F., Seidman, H.: The incidence and epidemiology of bronchogenic cancer, Proc. Fourth National Cancer Conference, J. B. Lippincott Co., Philadelphia, 1960, 319-322.

20. Doll, R.: Mortality from cancer among non-smokers, Brit. J. Cancer, 7:303-312, 1953.

21. Doll, R., Hill, A. B., Gray, P. G., and Parr, E. A.: Lung cancer mortality and the length of cigarette ends, Brit. M. J., 1:322-325, 1959. Dorn, H. F.: Tobacco consumption and mortality from cancer and other diseases, Acta Unio Internat. Contra Cancrum 16:1653-1665, 1950. Van Duuren, B. L.: Identification of some polynuclear aromatic hydrocarbons in cigarette-smoke condensate, J. Nat. Cancer Inst. 21:1-16, 1958.

22. Dunn, H. L.: Lung cancer in the twentieth century, J. Internat. Coll. Surgeons, 23:326-342, 1955.

23. Epidemiology of cancer of the lung: reports of study group. Tech. Rep. World Health Organ., 192:1-13, 1960.

24. Fraser, T. (1881), Edin. Med. J., 24, 577.

25. Gilliam, A. G.: Trends of mortality attributed to carcinoma of the lung: Possible effects of faulty certification of deaths due to other respiratory diseases, Cancer, 8:1130-1136, 1955.

26. Goldman, A.: Carcinoma of the lung of long duration, J.A.M.A., 118:354-364, 1942.

27. Graham, E. A., and Womack, N. A.: The problem of the so-called bronchial adenoma, J. Thoracic Surg., 14:106-127, 1945.

28. Graham, E. A.: Singer, J. J.: Successful removal of an entire lung for carcinoma of the bronchus, J.A.M.A., 101:137, 1933.

29. Great Britain, Medical Research Council: Tobacco smoking and cancer of the lung; Official statement, Brit. M. J., 1:1523, 1957.

30. Greenberger, R. A.: Mass survey detected lung cancer in Connecticut, Connecticut M. J., 20:857-863, 1956.

31. Guiss, L. W.: A 5-year follow-up of roentgenographically detected lung cancer suspects, Cancer, 13: 82-90, 1960.

32. Guiss, L. W., Kuenstler, P.: A retrospective view of survey photofluorograms of persons with lung cancer, Cancer, 13:91-95, 1960.

33. Haenszel, William, Loveland, Donald B., and Monroe, G. S.: Lung cancer mortality as related to residence and smoking histories. 1: white males, J. Nat. Cancer Inst., 28:947-997, 1962.

34. Haenszel, W., Shimkin, M. B., and Mantel, N.: Retrospective study of lung cancer in women, J. Nat. Cancer Inst., 21:825-842, 1958.

35. Halpert, B., Erickson, E. E., and Fields, W. S.: Intracranial involvement from cancer of the lung, A.M.A. Arch. Path., 69:93-103, 1960.

36. Hammond, E. C., and Garfinkel, L.: Smoking habits of men and women, J. Nat. Cancer Inst., 27:419-442, 1961.

37. Hammond, E. C., and Horn, D.: Smoking and death rates—report on forty-four months of follow-up of 187,783 men, J.A.M.A., 166:1159-1172 and 1294-1308, 1958.

38. Hammond, E. C.: Pollution, smoking and health, Texas State J. of Med., 58:639-647, 1962.

39. Harken, D. E., Black, H., Clauss, R., and Farrand, R. E.: A simple cervicomediastinal exploration for tissue diagnosis of intrathoracic disease, New Engl. J. Med., 251:1041-1044, 1954.

40. Hueper, W. C.: Environmental cancer of the lung, Acta Unio Internat. Contra Cancrum, 13:97, 1957.

41. Hueper, W. C.: Epidemiological, experimental and histological studies on metal cancers of the lung, Acta Unio Internat. Contra Cancrum, 15:424, 1959.

42. Hughes, F. A., Higgins, G.: Veterans Administration surgical adjuvant lung cancer chemotherapy study: Present status, J. Thor. & Card. S., 44:295-308, 1962.

43. Hughes, F. A., Jr., Pate, J. W., Campbell, R. E.: Bronchogenic carcinoma: Comparison of natural course and treatment with resection, x-radiation and nitrogen mustard, J. Thoracic & Cardiovas. Surg., 39:409-416, 1960.

44. Kirchoff, H., and Rigdon, R. H.: Cancer of the lung: The sex ratio; a review of the problem, Texas Rep. Biol. and Med., 17:29-48, 1959.

45. Koss, L. G., and Richardson, H. L.: Some pitfalls of cytological diagnosis of lung cancer, Cancer, 8:937-947, 1955.

46. Kotin, P., and Falk, H. L.: The role and action of environmental agents in the pathogenesis of lung cancer. 1: air pollutants, Cancer, 12:147, 1959.

47. Kreyberg, L., Saxen, E.: A comparison of lung tumor types in Finland and Norway, Brit. J. Cancer, 15: 211-214, 1961.

48. Kreyberg, Leiv: Main histological types of primary epithelial lung tumors, Brit. J. Cancer, 15:206-210, 1961.

49. McBurney, R. P., Kirklin, J. W., and Woolner, L. B.: Metastasizing bronchial adenomas, Surg., Gynec. & Obstet., 96:482-492, 1953.

50. McDonald, J. R., Moersch, H. J., and Tinney, W. S.: Cylindroma of the bronchus, J. Thoracic Surg., 14: 445-453, 1945.

51. Mersheimer, W. L., and Ederer, F.: End Results Evaluation of Cancer of the Lung and the Bronchus, Proc. Fourth National Cancer Conf., J. B. Lippincott Co., Philadelphia, 1960, 319-322.

52. Moersch, H. J., and McDonald, J. R.: Bronchial adenoma, J.A.M.A., 142:299-369, 1950.

53. Nickson, J.: Role of Radiation Therapy in Treatment of Carcinoma of the Lung, Proc. Fourth National Cancer Conference, J. B. Lippincott Co., Philadelphia, 1960, 315-317.

54. Ochsner, A., Ochsner, A., Jr., H'Doubler, C., Blalock, J.: Bronchogenic carcinoma, Dis. Chest, 37:1-12, 1960.

55. O'Neil, R. M., Lee, K. T., and Edwards, D. L.: Bronchogenic carcinoma: An evaluation from autopsy data, with special reference to incidence, sex ratio, histological type and accuracy of clinical diagnosis, Cancer, 10:1031, 1957.

56. Osler, Wm.: The Principles and Practice of Medicine, D. Appleton and Company, New York, 1892, 556-557.

57. Overholt, R. H.: The Surgical Treatment of Bronchogenic Cancer, Fourth National Cancer Conf. Proc., J. B. Lippincott Co., Philadelphia, 1960.

58. Paulson, D. L., Shaw, R. R., Kee, J. L., Mallams, J. T., Collier, R. E.: Combined pre-operative irradiation and resection for bronchogenic carcinoma, J. Thor. & Cardiovascular Surg., 44:281-294, 1962.

59. Poletti, T., and Riva, G.: Le manifestazioni osteoarticolari precoci in corso di neoplasie polmonari, Minerva Med., 49:750-758, 1958.

60. Posner, E., McDonald, L. A., and Cross, K. W.: Mass radiography and cancer of the lung, Brit. M. J., 1:1213-1218, 1959.

61. Proceedings—National Conference on Air Pollution, 1958, Washington, D. C., 1959, United States Government Printing Office.

62. Pryce, D. M., and Walter, J. B.: The frequency of gross vascular invasion in lung cancer with special reference to arterial invasion, J. Path. & Bact., 79:141-146, 1960.

63. Reid, J. M., Stevenson, J. G., Welsh, T. M., Barclay, R. S.: A survey of 372 patients operated on for lung cancer, Scottish Med. J., 6:443-448, 1961.

64. Rockey, E. E., Speer, F. D., Thompson, S. A., Ahn, K. J., and Hirose, T.: Experimental study on effect of cigarette smoke condensate on bronchial mucosa, J.A.M.A., 182:1094-1098, 1962.

65. Sabour, M. D., Osman, L. M., Glen, J., Fahy, T., Lamb, P.: Carcinoma of the lung, review of 509 cases, Diseases of the Chest, 41:530-546, 1962.

66. Salter, H.: Lancet, II, I, 1869.

67. Shaw, Robert R., Paulson, D. L., Kee, J. L., Jr.: Treatment of superior sulcus tumor by irradiation followed by resection, Ann. Surg., 154:29-40, 1961.

68. Shimkin, M. B., Connelly, R. R., Marcus, S. C., and Cutler, S. J.: Pneumonectomy and lobectomy in bronchogenic carcinoma—a comparison of end results of the Overholt and Ochsner Clinics, J. Thoracic and Cardiovas. Surg., 44:503-519, 1962.

69. Simons, E. J.: Primary Carcinoma of the Lung, The Yr. Book Pub., Inc., Chicago, 1937.

70. Smart, J., and Hilton, G.: Radiotherapy of cancer of the lung, results in selected groups of cases, Lancet, 1:880, 1956.

71. Spain, D.: Recent changes in relative frequency of various histologic types of bronchogenic carcinoma, J. Nat. Cancer Inst., 23:427, 1959.

72. Staszewski, J.: Smoking and Cancer in Poland, Brit. J. Cancer, 14:419-429, 1960.

73. Sunderman, F. W., Sunderman, F. W., Jr.: Nickel Poisoning: XI. Implication of nickel as pulmonary carcinogen in tobacco smoke, Am. J. Clin. Path., 35:203-209, 1961.

74. Walshe, W. H.: The physical diagnosis of diseases of the lungs, London, 1843, 285.

75. Walshe, W. H.: The diseases of the Lungs, Heart, and Aorta, Walton & Moberly, London, 1854, 554-555.

76. Wofford, J. L., Webb, W. R., Strauss, H. K.: Tuberculous scarring and primary lung cancer, Arch. S., 85:928-935, 1962.

77. World Health Organization: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Vol. 1, p 84, Geneva, W.H.O., 1957.

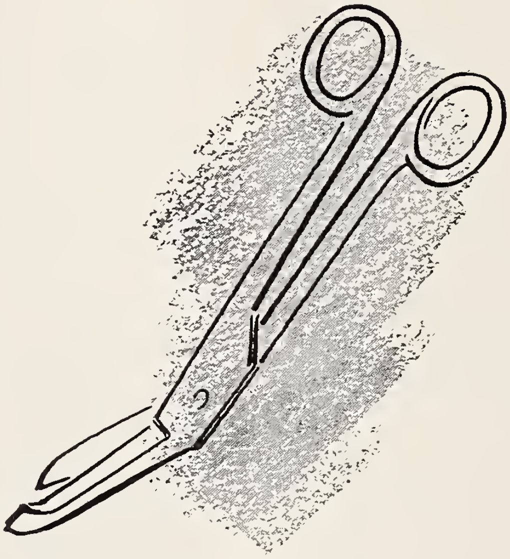
78. Wynder, E. L.: An appraisal of the smoking—lung—cancer issue, N.E.J.M., 264:1235-1240, 1962.

79. Wynder, E. L., Bross, I. J., Cornfield, J., and O'Donnell, W. E.: Lung cancer in women; study of environmental factors, New Engl. J. Med., 225:1111-1121, 1956.

80. Wynder, E. L., Graham, E. A., and Croninger, A. B.: Experimental production of carcinoma with cigarette tar, Cancer Research, 13:855-864, 1953.

81. Wynder, E. L., Lemon, F. R., and Bross, I. J.: Cancer and coronary artery disease among Seventh Day Adventists, Cancer, 12:1016-1028, 1959.

82. Yokoo, H., Suckow, E. E.: Peripheral lung cancers arising in scars, Cancer, 14: 1205-1215, 1961.



TRAFFIC ACCIDENTS

Chronic Medical Conditions As a Cause

JULIAN A. WALLER, M.D., M.P.H., *Berkeley*

■ *From comparatively scanty information, an increased traffic accident risk appears to be associated with several chronic medical conditions including alcoholism, cardiovascular disease, epilepsy, diabetes and mental illness. Further study probably will show that medical handicaps other than alcoholism are a factor in from 5 to 10 per cent of traffic accidents. However, in about half of the accidents caused by heart attacks, the individual has no previous knowledge of his illness, and prevention of the accident would not be possible. A selective program for identifying high risk drivers with medical conditions is feasible and warranted, but a program of mass medical examinations for all drivers is not.*

A very strong relationship has been shown between drunk driving and traffic accidents, and 50 to 75 per cent of all severe and fatal traffic accidents involve the use of alcohol. However, studies have shown that drivers with alcoholism rather than social drinkers represent the preponderance, but not the entirety, of those who get into trouble. A major reduction in the traffic accident toll may thus depend on the early identification and treatment of alcoholism.

THE RELATIONSHIP between chronic medical conditions and traffic accidents is a subject of considerable controversy. At one extreme the State of Pennsylvania has initiated a program of medical examinations for all drivers. At the other extreme any such program has been labeled as an exercise in futility. Dr. William Haddon, one of the country's leading accident researchers, has expressed doubt that the aggregate of medically precipitated traffic accidents is as great as many believe. Even if it were, he feels that adequate testing and regulatory procedures would be almost impossible to devise. One thing is certain: Opinion has far exceeded useful research.

Before examining some of the current practices, and the fact and opinion on which they are based, let us identify some of the human requirements for operating a motor vehicle. These can be divided into five categories:

1. A basic minimum of strength and mobility,
2. Ability to see and concentrate adequately on the roadway and traffic,
3. Ability to interpret and make judgements about real or impending changes in the traffic situation,
4. Knowledge of traffic laws,
5. Knowledge of the mechanics and, to a lesser extent, the physics of driving.

Presented at "Emergency Treatment: A Challenge to Physician and Citizen," University of California School of Medicine, 8 to 11 September 1965.

Bureau of Chronic Diseases, California Department of Public Health.

Submitted 16 May 1966.

Reprint requests to: Bureau of Chronic Diseases, State Department of Public Health, 2151 Berkeley Way, Berkeley, California 94704.

The medical aspects of driving fall into the first three categories. We can broadly divide medical disabilities into organic conditions which affect strength and movement, organic conditions which affect vision, concentration, and occasionally judgment, and psycho-social conditions which primarily affect interpretation and judgment. Several questions must be asked about these conditions and their relationship to accidents:

1. What proportion of the driving population can be expected to have these conditions?
2. What is the risk per vehicle-mile of having an accident resulting from the condition?
3. What proportion of the total number of accidents can be attributed to these conditions?
4. Can a program be devised to identify persons with an increased accident risk early enough in their driving experience to bring about a reduction in accidents?
5. If these persons can be identified, can the motor vehicle departments regulate their driving in such a manner as to reduce accidents?

Each of these questions has been the subject of wide disagreement. Perhaps the easiest to answer, however, is the first. The medical literature is replete with estimates of the number of persons with various medical conditions. The National Health Survey and the California Health Survey have provided useful information about the number of conditions to be expected in persons of driving age. Based on these, West[9] estimated in 1963 that in California there were 100,000 persons of driving age with heart disease, 40,000 with epilepsy, 80,000 with diabetes, 160,000 with a history of admission to a state mental hospital during the preceding 10 years, 700,000 problem drinkers, 410,000 with orthopedic handicaps and 630,000 with impaired vision or hearing. In California, about 85 per cent of the driving age population is licensed, and one might expect a somewhat lesser percentage among persons with medical conditions. Probably a reasonable estimate is that at least 15 per cent of drivers have one or more of the above conditions other than alcoholism and 6 per cent have alcoholism.

The question of risk of an accident per vehicle-mile is still very much unanswered. Only two studies[3,5] have been done in which the number of miles of driving was taken into consideration. In one of them[3] it was found that drivers with alcoholism had twice as many accidents per vehicle-mile as did other drivers. Our study of persons with medical conditions who were known to the California Department of Motor Vehicles[5] showed that drivers with heart disease, stroke, epilepsy, diabetes, mental illness and alcoholism had approximately twice as many accidents per vehicle-mile as did a group of drivers not known to have these conditions. Drivers who had been convicted for illegal use of drugs had almost twice as many violations, but no more accidents, than did drivers in the comparison sample. It must be emphasized that this study is of persons already known to the Department of Motor Vehicles, and no conclusions can be drawn about the accident risk of persons not known to the motor vehicle authorities.

The actual proportion of medical episodes in the total number of accidents currently is unknown, but it is possible to estimate the probable maximum and minimum percentages to be expected. If one were to use our figures for the California sample described above, and were to apply them to the unreported drivers with these conditions, the maximum proportion of traffic accidents attributable to chronic medical conditions (other than alcoholism, which will be discussed later) would be 15 per cent. In other words, 15 per cent of the drivers could be expected to have 30 per cent of the accidents, of which half would be attributable to a medical condition. A recent study from Canada[10] suggests that 3 to 4 per cent of accidents are caused by medical episodes. I suspect that further studies ultimately will reveal that chronic medical conditions other than alcoholism are a factor in from 5 to 10 per cent of all traffic accidents. While this is not a very large proportion of the accidents, it may add up to from 2,000 to 4,500 deaths a year and many thousands of injuries for the entire country.

But is it possible to identify these drivers before they have too many accidents? Pennsylvania has initiated a program of medical examinations for all drivers by their family physician. We do not feel that such a system is warranted because in California it would require 17,000 medical examinations a day, and because physicians, while quite concerned about traffic safety, often tend to underestimate the extent to which their own patients have a handicap to driving. In addition, for about half of the traffic accidents involving a heart attack, the individual did not know previously that he had heart disease.[1]

The California system, like that in several other states, requires that physicians must report any patient who has recurring episodes of loss of consciousness, and that everyone who applies for a license or for renewal must indicate whether he has had such episodes or any other condition which may handicap his driving. In our recent study[5] we found to our surprise that, in California, at least 75 per cent of the new cases of epilepsy in adults, and fewer cases of other medical conditions, were being reported to the Department of Motor Vehicles through these two mechanisms and through reporting of people who have had an accident because of a medical episode.

Kentucky, following a modification of recent American Medical Association recommendations, is evaluating a new system for identifying drivers with a medical handicap. Medical examinations are required in three types of situations:

1. When a license applicant has an obviously impaired physical function,
2. When a driver has had three accidents within a 24-month period,
3. When a driver suggests that he "blacked out" or that medical problems contributed to his accident.

The initial evaluation of this program indicated that at least half of the drivers with three accidents in two years were found to have a serious medical condition. It is our feeling that a selective screening program, such as is used in California, Kentucky and several other states, is more realistic than is the Pennsylvania approach.

What to do with the impaired driver, once identified, presents still another problem. While the driving license legally is considered a privilege, in many areas of the state it also is almost a necessity. In California, persons with medical handicaps who come to the attention of the Department of Motor Vehicles are interviewed, and information from their physician is carefully reviewed, sometimes with the aid of the local medical society traffic safety committee. About 50 per cent of the drivers are deemed to have a sufficient handicap to require revocation of the license for a time. Many of these persons have the license returned if their condition improves. However, they are still kept under close medical surveillance. This system appears to be working well and it is followed in many other states also.

The subject of drinking and driving deserves special attention. Many studies have been done which strongly implicate alcohol in traffic accidents, but only eight meet good research requirements by having a comparison sample and by comparing accidents during a similar amount of driving exposure. These studies, discussed in a recent communication,[7] revealed that:

1. There is a strong association between the use of alcohol and the occurrence of traffic accidents. With a blood alcohol level of 100 mg per 100 ml (0.10 per cent by weight) the risk of having an accident is increased about 10 times. At 150 mg per 100 ml, the risk is increased 25 to 50 times. This increase in risk has been shown for drinking drivers, for persons known to have alcoholism, and for pedestrians.

2. Somewhere between 50 and 75 per cent of all fatal traffic accidents involve the use of alcohol. Since alcohol-related accidents tend to be more severe than accidents not involving drinking, the proportion of fatal accidents involving alcohol is much greater than the proportion of minor accidents involving alcohol.

3. It can be shown by laboratory studies that many persons are impaired with blood alcohol at 50 mg per 100 ml and that virtually everyone is impaired at 100 mg per 100 ml. However, in the vast majority of traffic fatalities involving alcohol the levels are much higher than that. In fact, the average in many studies is above 200 mg per 100 ml, a level at which most social drinkers would be "under the table."

This last fact has led a number of investigators to suspect that the major portion of the traffic accident toll where drinking is involved may well be associated with alcoholism rather than with social drinking. The various data to support this were recently reviewed.[6] It is well known that the very heavy drinker develops a substantial tolerance to intoxication, but only a minimal tolerance to impairment, and that it is possible for such a person to manipulate an automobile—although very poorly—when the average drinker would be so intoxicated that he could not even stand or remain conscious. Payne and Selzer, in a fascinating study,[2] suggested that drivers known to be alcoholic become more reckless in their driving after drinking, while social drinkers become more cautious. They also found,[4] in psychiatric interviews of 67 drunk drivers and their wives, that 72 per cent of the drivers were alcoholic. We are doing a similar study to find simpler methods than a psychiatric interview to screen drunk drivers for alcoholism. A study of driver and pedestrian fatalities in San Francisco[8] has shown that 15 per cent of adults who were sober at the time of the accident had fatty changes or cirrhosis of the liver, whereas 62 per cent of those who had blood alcohol levels of 150 mg or more per 100 ml had such changes. Almost three quarters of the fatally injured persons who had been drinking had alcohol levels in this range.

Since it now appears that many of the traffic deaths are related to alcoholism rather than to the social use of alcohol, we can indeed say that chronic medical conditions play a very major part in our traffic toll. However, the key to control will not be a more punitive approach to the drinking driver but rather the recognition at an early point that he really is a driving drinker who needs referral to proper rehabilitation facilities if his compulsive drinking pattern is to change. Simultaneously, the heavy fine or the six-month suspension of the license of such a person must be replaced by an open-ended revocation of license until the condition improves.

Can such a system work? Never has it really been tried, but many workers in the field of alcoholism have observed that often it takes a major personal crisis to motivate the compulsive drinker to seek treatment. Judging from the anguish expressed by most people when the possibility of losing a license arises, revocation is indeed such a crisis.

REFERENCES

1. Myerburg, R. J., and Davis, J. H.: The medical ecology of public safety. 1. Sudden death due to coronary heart disease, Am. Heart J., 65:586-595, November 1964.

2. Payne, C. E., and Selzer, M. L.: Traffic accidents, personality and alcoholism: Preliminary study, J. Abd. Surg., 4:21-26, January 1962.

3. Schmidt, W., Smart, R. G., and Popham, R. E.: The role of alcoholism in motor vehicle accidents, Traffic Safety Research Rev., 6:212-217, December 1962.

4. Selzer, M. L., Payne, C. E., Gifford, J. D., and Kelly, W. L.: Alcoholism, mental illness and the "drunk driver," Am. J. Psychiat., 120:326-331, October 1963.

5. Waller, Julian A.: Chronic medical conditions and traffic safety: A review of California experience, New Engl. J. Med., 273:1413-1420, 23 December 1965.

6. Waller, Julian A.: Implications of shifting emphases on alcohol use and traffic accidents, presented at 4th International Conference on Alcohol and Traffic Safety, Indiana University, Bloomington, 6 to 10 December 1965.

7. Waller, Julian A.: Alcohol and traffic accidents: Can the Gordian knot be broken? Traffic Safety Research Rev., 10:14-21, March 1966.

8. Waller, J. A., and Turkel, H. W.: Alcoholism and traffic deaths, to be published in New Engl. J. Med.

9. West, Irma: The impaired driver—A critical review of the facts, Calif. Med., 98:271-274, May 1963.

10. Williams, Norman: Traffic accidents—epidemiology and medical aspects of prevention, Canad. Med. Assn. J., 90:1099-1104, 9 May 1964.

REVIEW ARTICLE

Protein-Losing Gastroenteropathy

MARTIN A. POPS, M.D., *Los Angeles*

■ *In the past 10 years with the development of improved methods, particularly radioisotope techniques, it has been demonstrated that a number of patients with gastrointestinal disease and depletion of plasma proteins become hypoproteinemic because of actual leakage of albumin and other plasma proteins into the lumen of the gastrointestinal tract. The site of protein leakage is variable depending on the underlying pathological state but the loss of protein-containing lymph through the gastrointestinal lymphatic channels seems to be the major mechanism for hypoproteinemia.*

It has become apparent that there exists a normal mechanism for secretion of plasma proteins into the gastrointestinal tract as part of the overall metabolism of the plasma proteins. When the process is exaggerated so that resynthesis of plasma protein cannot keep pace with its degradation, sometimes severe hypoproteinemia is the result. Such a pathological process has now been described in approximately 40 disease states. A review of all the techniques which can demonstrate gastroenteric protein loss reveals that there are no widely available quantitative tests but that accurate quantitation is not necessary for the diagnosis of protein losing gastroenteropathy.

FOR MANY YEARS it was assumed that the hypoproteinemia occurring in patients with gastrointestinal disease was secondary to impaired synthesis of proteins because of malnutrition and resultant poor intake and assimilation of dietary protein. During the past few years the availability of isotopically labeled proteins has led to a more complete understanding of the role of the gastrointestinal tract in the metabolism of plasma proteins in health and certain disease states. A number of disease entities are now known to result in actual leakage of plasma protein into the gut. The new techniques, in fact, have demonstrated that many hypoalbuminemic and hypoglobulinemic patients are actually synthesizing a normal or increased amount of serum proteins but are losing them into the gastrointestinal lumen. There they are catabolized quickly into constituent amino acids which are just as quickly reabsorbed and again made available to the body's mechanism for resynthesis of protein. Hypoproteinemia therefore results when the rate of catabolism due to leakage exceeds the rate of synthesis—a sort of "wheel spinning" protein dysplasia.

Physiology in Health and Disease

By various means it has been shown that plasma protein is normally secreted into the gut. Electrophoresis has demonstrated serum albumin in gastric juice in normal persons in a concentration varying from 200 mg to over 400 mg per 100 ml.[7] Capillary tube precipitation and agar diffusion

---

From the Division of Gastroenterology, Department of Medicine, UCLA School of Medicine, Los Angeles 90024.

Reprint requests to: Division of Gastroenterology, Department of Medicine, UCLA School of Medicine, Los Angeles, California 90024.

have identified both plasma albumin and globulin in intestinal juice in man, and radioautographs in animals show that serum albumin accumulates and is excreted in the upper part of the small intestine.[17] It appears that a normal man has an average daily breakdown of 12 gm of albumin (100 per cent), of which about 10 to 30 per cent is degraded in the stomach and between 4 and 6 gm (33 to 50 per cent) is catabolized in the duodenum and jejunum. As much as 9 gm or 75 per cent of the total albumin catabolized daily is eliminated by the stomach and duodenum. It is evident that a significant proportion of the daily breakdown of albumin occurs within the gastrointestinal tract.

Plasma proteins can escape from the intravascular compartment and their presence in other body fluids is well known. However, the mechanism whereby proteins enter the gastrointestinal tract is not understood. In certain inflammatory or neoplastic diseases such as ulcerative colitis or cancer of the stomach, the exudate from the inflammatory process or material shed from the tumor understandably contains plasma proteins.

In other conditions, the pathway from interstitial fluids into the intestine in unknown. A certain amount may diffuse passively through the intercellular spaces of mucosal cells. However, the lymphatic channels of the gut appear to be intimately involved and it is an interesting hypothesis that an increase in hydrostatic pressure within the lymphatic system can increase the protein loss. In patients with gastrointestinal protein loss the half life of survival of albumin as well as a variety of globulins including 7S-γ-globulin (IgG), γ-macroglobulin (IgM), β-2-A-globulin (IgA), and ceruloplasmin[23] is decidedly reduced.

Normal subjects catabolize from 5 to 11 per cent of their intravascular pool of albumin or γ-globulin each day but patients with gastrointestinal loss may catabolize over 60 per cent of their plasma pool of these proteins daily, with the excess over normal presumably lost into the gastrointestinal tract. In patients losing serum proteins into the gastrointestinal tract it would appear that all the proteins including the 19S-macroglobulins pass through and are degraded at the same rate irrespective of molecular size.[24]

For the most part, the proteins thus lost into the alimentary lumen are catabolized into their constituent amino acids and quickly reabsorbed. Hypoproteinemia results when the rate of loss and intraluminal degradation exceeds the body's maximal rate of protein synthesis. It follows, then, that those proteins with the longest normal survival are those whose concentration is the most severely depressed. Thus serum concentrations of albumin and γ-globulin are lowest in the disease states associated with protein loss. Other serum proteins such as transferrin and macroglobulins are less markedly depressed.[10] The synthetic rate of albumin in patients with gastrointestinal protein loss is normal or increased to a maximum of twice normal and the rate of synthesis of the three major immunoglobulins (IgG, IgA, IgM) is usually normal in patients with protein loss unassociated with a severe inflammatory disease. This differs from the usual accelerated immunoglobulin synthesis seen following antigenic stimulation. It would appear that a low plasma concentration is not an effective stimulus to immunoglobulin production.[24]

Methods of Demonstrating Protein Leakage Into Gastrointestinal Tract

Intubation

The recovery of high quantities of proteins from the stomach and small bowel originally demonstrated the existence of this mechanism of protein loss. Citrin and coworkers,[3] in 1957, first conclusively showed that excessive loss of albumin into the stomach may occur in disease and that this loss may greatly diminish the concentration of serum albumin, resulting in edema. These phenomena were noted in a patient with giant hypertrophy of the gastric mucosa sometimes called Menetrier's disease. Subsequently, Holman and coworkers[9] demonstrated that serum albumin and γ-globulin are normally secreted into the gastrointestinal tract and that the albumin loss is increased in certain intestinal diseases.

Although such techniques were of great importance historically, the technical difficulties of intubation and the variable degrees of degradation by enzymes during the aspiration procedures make quantitative assessment of the magnitude of protein loss into the gut all but impossible. Intubation techniques were thus quickly supplanted by other methods of evaluating alimentary protein loss.

Nitrogen Balance Techniques

In 1949 Albright and coworkers[1] described a nitrogen, calcium and phosphorus metabolic balance technique to study the fate of intravenously administered unlabeled human serum albumin. They were able to demonstrate for the first time that idiopathic hypoalbuminemia could be caused by excessive protein catabolism rather than defective protein synthesis. Balance studies, however, are complex and laborious, requiring the use of highly disciplined clinical and laboratory technicians and the expenditure of much time. Studies since then have shown that spuriously normal values for protein catabolism may be obtained with the use of this technique.[2]

Radioiodinated Serum Albumin

Using intravenously administered radioiodinated albumin, one may determine by dilution the plasma volume and the total body albumin pools. The decline in radioactivity in the serum and whole body of radioiodinated serum albumin (RISA) gives a measurement of albumin degradation and in the steady state, the rate of albumin synthesis. Patients with gastrointestinal protein loss have reduced circulating and total body pools of albumin, a normal or increased rate of albumin synthesis, and a decidedly shortened albumin survival.[10,25]

The major limitation of this technique is that data so obtained from serum and urinary radioactivity curves only shows that rapid catabolism is the cause of the hypoproteinemia and the gastrointestinal tract cannot be implicated as the site of protein loss. This is because of the rapid reabsorption of the I^{131} label following its passage with albumin into the lumen of the gut. There is also active secretion of radioiodine into the intestine via salivary, gastric and small bowel secretions. Measurement of fecal I^{131} is usually very low in even severe disease states associated with albumin loss into the gastrointestinal tract, since most of the radioiodine entering the bowel is reabsorbed and excreted free in the urine. Moreover, it might be expected that fecal content of I^{131} would be higher in patients with severe diarrhea or those with lesions low in the gastrointestinal tract, instances in which there might not be time to reabsorb the label.

In an effort to solve the problem of I^{131} reabsorption from the gut after intravenous RISA administration, Jeejeebhoy and Coghill[11] fed Amberlite IRA-400, an ion exchange resin which was meant to bind the radioiodine released by the lost and catabolized RISA once it entered the gut. This refinement subsequently failed to add to accurate quantitative data since it was shown that the resin did not trap all radioiodine liberated in the bowel. Only 35 per cent of the radioactivity of orally administered RISA given with resin was excreted in the stool while 65 per cent was excreted in the urine.[6] The technique was also hampered by the secretion of non-protein bound radioiodine into the gastrointestinal tract, making this unsuitable for accurate quantitative measurements.

I^{131} Polyvinylpyrrolidone (Fecal I^{131}-PVP)

Since there is error inherent in RISA measurements as described above, Gordon[8] in 1959 introduced the I^{131}-PVP test The substance is a polymer with a molecular weight of approximately 40,000. When labeled with I^{131} and given orally, more than half usually appears in the feces. It was argued that if this substance be given intravenously, it could leak through that part of the gastrointestinal epithelium which is permeable to albumin, considering its similar size. It was also noted that since it was a polymer it could not be digested or absorbed. As the test is performed, the thyroid gland is blocked with inorganic iodine to prevent thyroidal uptake of the label. After the PVP has been dialyzed to remove free iodine, it is injected intravenously and fecal radioactivity for the next four days is determined. Normally, less than 1.5 per cent of the PVP is excreted in the feces ,whereas gastrointestinal protein losers excrete more of the macromolecule, with up to 32 per cent of the administered dose having been reported in disease states.[8]

This test has afforded an excellent qualitative measure of protein loss but does not provide a quantitative measurement. It has the disadvantage of variable molecular size and naturally, its distribution and catabolism differ from that of albumin. For these reasons I^{131}-PVP must be considered, at best, a useful qualitative indicator of protein loss via the gut.

Chromium^{51}-Labeled Albumin

Many of the advantages and limitations of the PVP test apply to the more recent use of the Cr^{51} labeled albumin test. It was noted in studying quantitative measurement of gastrointestinal blood loss, that Na_2Cr^{51} and $Cr^{51}Cl_3$ were practically unabsorbable from the lumen of the gut and when injected were not normally excreted into the gastrointestinal tract. Though sodium chromate would effectively label albumin when incubated with plasma.[5] Subsequently, direct intravenous administration of unbanded $Cr^{51}Cl_3$ with subsequent *in* *vivo* chelation was used. If protein leakage into the gut were to occur, Cr^{51} should be recoverable and easily measured in the feces. Utilizing Cr^{51}-albumin intravenously in eight patients with enteric protein loss previously demonstrated with I^{131}-albumin and PVP tests, Waldmann[18] demonstrated excretion of 2.1 to 4.2 per cent of the initial dose per day collection as compared to maximum control values of 0.63 per cent. It was also suggested that with Cr^{51} the site of leakage could be localized by intubation. This technique, nevertheless, remains largely qualitative. The rate of degradation of Cr^{51}-labeled albumin is greater than that of native albumin or I^{131}-albumin and its plasma disappearance does not thus reflect true albumin catabolism. Most likely the rapid degradation is due to denaturation of the protein by the radiochromium.

Copper^{67}-Labeled Ceruloplasmin

Much more recently studies using Cu^{67}-ceruloplasmin have been carried out and show that this test may be quiet useful for quantitation of gastrointestinal protein loss. Following oral administration, from 80 to 100 per cent of the substance appears in the stool, indicating that absorption is minimal. After intravenous administration it was determined that about 20 per cent of the circulating ceruloplasmin pool in man is catabolized daily. In normal persons only 2 per cent of the pool of Cu^{67}-ceruloplasmin was excreted into the stool daily. In patients with documented enteric protein loss, 17 to 45 per cent of the circulatory Cu^{67}-ceruloplasmin pool was lost into the gastrointestinal tract each day.[23] This test is not widely available although it fulfills the criteria for an accurate label for quantitative estimation of enteric protein loss. At present the preparation of the Copper^{67} is difficult and the cost is almost prohibitive.

In summary, from the clinician's standpoint, it would seem that of all the tests currently available, the Cr^{51} technique with direct intravenous injection of chromic^{51} chloride is probably the method of choice on the basis of safety, simplicity and availability.

Despite the flurry of interest in the phenomenon of gastrointestinal protein leakage, the reader should not lose sight of the fact that most patients with gastrointestinal disease and hypoalbuminemia probably become protein depleted on the basis of insufficient anabolism (decreased synthesis) of plasma proteins. Thus, patients with severe liver disease may not be able to make sufficient quantities of protein. The patient with cachexia of cancer, the postgastrectomy patient, the person with severe pancreatic insufficiency or chronic inflammatory disease of the bowel—all may become protein depleted but usually on the basis of exogenous or endogenous starvation and not because of leakage of protein into the gastrointestinal tract. However, a rapidly growing list of diseases has been associated with excessive gastrointestinal protein loss. In many of these disease states the phenomenon of hypoproteinemia due to decreased synthesis may combine with increased catabolism by loss to cause the patient double jeopardy.

Diseases Associated with Protein-Losing Gastroenteropathy

Excessive protein loss into the gastrointestinal tract has now been demonstrated in association with more than 40 varied disease entities.[19] Space does not herein permit a completely referenced accounting of all the disorders. Some are quite rare. Certain groupings are possible according to the mechanism or proposed mechanism of the protein loss (Table I).

The terms *primary* and *secondary* are of little or no use in the understanding of these disorders and should be discarded. In the past the term *primary protein losing gastroenteropathy* has been used to describe those entities with hypoalbuminemia and edema as the major manifestations with little gross gastrointestinal disease. Patients with this disorder were originally classified as having "iodiopathic hypoproteinemia." It is now recognized that these patients often have intestinal lymphangiectasia. The "secondary protein losing enteropathies" included all the remainder of the disorders, those with recognizable gastric or enteric pathologic changes. In these, the clinical features were usually those of the underlying disease, the protein loss being of varying significance in the clinical manifestations.

Intestinal Lymphangiectasia

In the past few years, the greatest proportion of those patients, most often in the pediatric age group, who were formerly categorized as having idiopathic or hypercatabolic hypoproteinemia, have now been found to have the newly described syndrome of intestinal lymphangiectasia. This disorder is characterized by severe, often asymmetrical edema, hypoproteinemia and lymphocytopenia. Histologically there is a generalized disorder of lymphatic channels, including dilated lymphatic vessels of the small intestinal submucosa. It is by no means a common disorder but it is being recognized with increasing frequency. Over 40 patients with intestinal lymphangiectasia and documented gastrointestinal protein loss have been reported.[13,14,20,21,25] Some of the patients have a sclerotic lesion of mesenteric lymphatic vessels and lymph nodes associated with dilatation of lymphatic vessels on the bowel serosa as well as the submucosa.

It has been speculated that some of these lymphatic channels may burst, producing leakage of lymph into the lumen of the intestine. This lesion may often be found on peroral biopsy of the small intestine but even if no abnormality is noted on biopsy, this does not exclude the diagnosis. In several patients dilated lymphatic channels were observed at laparotomy. Albumin concentration in lymph is between 2 and 3 gm per 100 ml. It has been estimated that at least 48 gm of albumin passes through the gastrointestinal lymphatic channels daily. If a significant leakage occurs, it is readily apparent why a patient would rapidly become hypoproteinemic.

TABLE 1.—*Disorders Associated with Gastroenteric Loss of Protein*

Neoplastic Diseases
- Esophageal carcinoma
- Gastric carcinoma
- Gastric polyps
- Lymphosarcoma
- Tuberous sclerosis with small bowel angiomas
- Colonic carcinoma and villous adenoma

Non-specific Inflammatory Diseases
- *Giant rugal hypertrophy of the stomach (Menetrier's disease)
- Atrophic gastritis
- Gluten-induced enteropathy (non-tropical sprue)
- Tropical sprue
- *Crohn's disease (regional enteritis)
- Non-specific granuloma of bowel
- Chronic pancreatitis
- *Ulcerative colitis
- Congenital megacolon associated with enterocolitis or exudative enteropathy
- Associated with angioneurotic edema
- "Allergic" gastroenteropathy

Infections of the Gastrointestinal Tract
- Whipple's disease
- Chronic gastrointestinal tuberculosis
- Acute gastrointestinal (bacterial or viral) infection
- Hookworm infection

Congenital or Acquired Anatomic Abnormalities
- Postgastrectomy syndrome
- Gastrocolic fistula
- Jejunal stenosis
- Jejunal diverticulosis
- *Intestinal lymphangiectasia
- Fistula between thoracic duct and small bowel

Non-Gastrointestinal Diseases
- *Congestive heart failure, constrictive pericarditis
  - Interatrial septal defect
  - Familial myocardiopathy
  - Inferior vena cava thrombosis
- *Agammaglobulinemia
- Nephrotic syndrome
- Retroperitoneal fibrosis

*Disorders discussed in text.

The foregoing explanation for lymph leakage in this disorder would also account for the lymphopenia which is also commonly seen. This postulated mechanism has not yet been proven. Chylous effusions, diarrhea, steatorrhea, abdominal pain and even blindness secondary to macular edema have been reported to be associated with the disease. As a group, the patients seem to have the most severe protein loss of all the protein-losing enteropathies, a loss comparable in magnitude to that of patients with severe nephrotic sydrome.

The pathogenesis of the lymphatic abnormalities remains obscure. In some patients with onset in neonatal life and a family history of hypoproteinemia and chylous effusions, a congenital malformation of the lymphatic channels is a likely explanation. In other cases, acquired obstruction of these channels, with subsequent increase in hydrostatic pressure and dilatation, has been postulated.

Treatment of these patients is extremely difficult. Recently it was shown that rapid albumin catabolism was decreased in a subject placed on a low fat diet.[12] It is known that fatty acids of medium chain length, that is, containing eight to 12 carbon atoms, are absorbed mainly into the portal venous system and not via the intestinal lymphatic channels. It seems reasonable to assume that a diet low in long-chained fatty acids might spare the intestinal lymphatic channels and so result in decreased chylous leakage into the gut. A few patients treated in this way have had apparent improvement in serum protein levels and decrease in edema. This exciting prospect awaits further clinical trial.

Giant Rugal Hypertrophy of the Stomach

Giant rugal hypertrophy of the stomach is of historical interest. It was in this condition that Citrin and his coworkers[3] in 1957 first demonstrated that excessive loss of albumin into the gut could cause a hypercatabolic state and hypoalbuminemia. The cause of the excessive protein loss into the stomach in this condition is uncertain. The clinical features may be those of mild to severe postprandial "indigestion," which may cause weight loss. The patient may have severe hypoproteinemia and resultant edema when first seen. The diagnosis is usually suspected when huge gastric rugae are seen radiographically. These patients seldom, if ever, have hypersecretion of hydrochloric acid. The abnormalities in plasma protein metabolism may improve after subtotal gastrectomy. Surgical operation would seem to be indicated for these patients with severe hypoproteinemia, documented gastrointestinal protein loss by one or more of the recognized techniques (vide supra), characteristic radiographic changes on barium contrast examination of the gastrointestinal tract and no other recognizable disorder affecting albumin metabolism.

Non-specific Inflammatory Diseases

An important cause of protein loss into the gastrointestinal tract is the exudation commonly seen in patients with active Crohn's disease and ulcerative colitis. Patients with these diseases may lose protein as the major mechanism of hypoproteinemia. Decreased synthesis of plasma proteins which could be the result of impaired hepatic function, malabsorption or malnutrition due to deficient protein intake, can also be seen. The mechanism of protein loss into the bowel seems to be relatively simple considering the pathologic changes of the process, that is, chronically inflamed, ulcerated tissue from which pus and blood exude. The treatment of this form of protein loss is that of the underlying disease.

Congestive Heart Failure

Although the mechanism has not been fully elucidated, hypoproteinemia due to enteric plasma protein transudation has been described in a number of patients with congestive heart failure.[4] It was suggested that this was caused by a functional disorder of intestinal lymphatic channels secondary to an increase in central venous pressure. That this is quite likely is supported by the observations that patients with constrictive pericarditis seem particularly prone to this phenomenon and that signficant increases in thoracic duct pressures and flow rates were measured in such patients.[15] Protein-losing enteropathy has been reported to disappear following successful pericardectomy. Clinical recognition of hypoproteinemia in patients with severe right-sided congestive failure can be very difficult, since a major manifestation of both congestive cardiac failure and protein-losing enteropathy is edema. Significant hypoalbuminemia in patients with congestive heart failure should alert the clinician to the possibility of enteric protein loss.

Agammaglobulinemia

Twenty-four patients with defective γ-globulin synthesis were studied by Waldmann and Laster.[22] The serum albumin concentration was below 3.6 gm per 100 ml in 20 of the 24. Six of these patients were studied with I^{131}-albumin and I^{131}-PVP, and excessive loss of albumin was demonstrated in three. Although it was thought that these three patients were primarily hypogammaglobulinemic, one had a sprue-like syndrome, another was described as having iliocolitis, and the third had persistent positive stool cultures for salmonella Newport. It was felt that the primary defect of γ-globulin synthesis led secondarily to disorders of the gastrointestinal tract and consequent enteric loss of the serum proteins. More recently,[16] a patient with severe hypoproteinemia, enteric loss of protein (high fecal Cr^{51} after labeling) and chronic diarrhea was studied with respect to globulin synthesis. No plasma cells were found in the aspirated bone marrow. Quantitative determination of serum immunoglobulins showed pronounced depression of IgG and moderate depression of IgA and IgM. Peripheral blood lymphocytes in this patient, when incubated with antihuman immunoglobulin serum, failed to demonstrate immunofluorescence, suggesting that they were indeed defective in immunoglobulin synthesis. This, then, would seem to suggest that patients with protein-losing enteropathy may become albumin and globulin deficient due to leakage of the plasma proteins into the gastrointestinal tract, but that patients with acquired or congenital hypogammaglobulinemia may also become plasma protein deficient for the same reason. The mechanism has not been elucidated but it seems possible that in such patients chronic, low grade infections or infestations of the alimentary tract with subsequent leakage of proteins can develop.

REFERENCES

1. Albright, F., Bartter, F. C., and Forbes, A. P.: The fate of human serum albumin administered intravenously to a patient with idiopathic hypoalbuminemia and hypoglobulinemia, Trans. Ass. Amer. Physicians, 62:204-213, 1949.

2. Bartter, F. C., Steinfeld, J. L., Waldmann, T., and Delea, C. S.: Metabolism of infused serum albumin in the hypoproteinemia of gastrointestinal protein loss and

in analbuminemia, Trans. Assn. Amer. Physicians, 74: 180-194, 1961.

3. Citrin, Y., Sterling, K., and Halstead, J. A.: Mechanism of hypoproteinemia associated with giant hypertrophy of gastric mucosa, New Engl. J. Med., 257:906-912, 1957.

4. Davidson, J. D., Waldmann, T. A., Goodman, D. S., and Gordon, R. S., Jr.: Protein-losing gastroenteropathy in congestive heart failure, Lancet, 1:899-902, 1961.

5. Ebaugh, F. J., Jr., Rodman, G., and Peterson, R. E.: Quantitative measurement of gastrointestinal blood loss, Am. J. Med., 25:169-179, 1958.

6. Freeman, J., and Gordon, A. H.: The measurement of albumin leak into the gastrointestinal tract using I^{131}-albumin and ion exchange resin by mouth, Gut, 5:155-157, 1964.

7. Glass, G. B., and Ishimori, A.: A pasage of serum albumin into the stomach: its detection by paper electrophoresis of gastric juice in protein-losing gastropathies and gastric cancer, Am. J. Digest. Dis., 6:103-133, 1961.

8. Gordon, R. S., Jr., Bartter, F. C., and Waldmann, T.: Idiopathic hypoalbuinemias, Ann. Int. Med., 51: 553-576, 1959.

9. Holman, H., Nichel, W. F., Jr., and Sleisenger, M. H.: Hypoproteinemia antedating intestinal lesions and possibly due to excessive serum protein loss into the intestine, Am. J. Med., 27:963-975, 1959.

10. Jarnum, Stig: Protein-losing gastroenteropathy, Blackwell Scientific Publications, Oxford, 1963.

11. Jeejeebhoy, K. N., and Coghill, N. F.: The measurement of gastrointestinal protein loss by a new method, Gut, 2:123-130, 1961.

12. Jeffries, G. H., Chapman, A., and Sleisenger, M. H.: Low fat diet in intestinal lymphangiectasia; effect in albumin metabolism, New Engl. J. Med., 270:761-764, 1964.

13. Larson, D. L., Bond, T. P., Rodin, A. E., Coers, C. R., and Lewis, S. R.: Clinical and experimental obstruction of the thoracic duct, Surgery, 60:35-42, 1966.

14. McDonogh, T. J., Gueft, B., Pyun, K., and Arias, I. M.: Hypoproteinemia, chylous ascites, steatorrhea and protein-losing enteropathy due to chronic inflammatory obstruction of major intestinal lymph vessels, Gastroenterology, 48:642-647, 1965.

15. Peterson, V. P., and Ottosen, P.: Albumin turnover and thoracic-duct lymph in constrictive pericarditis, Acta Med. Scand, 176:335-344, 1964.

16. Pops, M. A., and Winkelstein, A.: Unpublished observations.

17. Ullberg, S., Birke, G., Ewaldsson, B., Hansson, E., Liljedahl, S. O., Plantin, L. O., and Wetterfors, J.: The role of the gastrointestinal tract in the elimination of serum albumin, Acta Med. Scand., 167:421-427, 1960.

18. Waldmann, Thomas A.: Gastrointestinal protein loss demonstrated by Cr^{51}-labeled albumin, Lancet, 2: 121-123, 1961.

19. Waldmann, Thomas A.: Protein-losing enteropathy from Progress in Gastroenterology, Gastroenterology, 50:422-443, 1966.

20. Waldmann, Thomas A.: The specific syndrome of intestinal lymphangiectasia, Ross Conference on Macromolecular Aspects of Protein Absorption and Excretion in the Mammalian Intestine, Columbus, Ohio, 94-105, 1965.

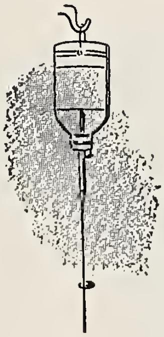
21. Waldmann, T. A., Gordon, R. S., Jr., Dutcher, F. F., and Wertlake, P. T.: Syndromes of gastrointestinal protein loss from Plasma Proteins and Gastrointestinal Tract in Health and Diseases, Ejnar Munksgaards Forlag, Copenhagen, 156-160, 1962.

22. Waldmann, T. A., and Laster, L.: Abnormalities of albumin metabolism in patients with hypogammaglobulinemia, J. Clin. Invest., 43:1025-1035, 1964.

23. Waldmann, T. A., Morrel, A. B., Wochner, R. D., and Sternlieb, I.: Quantitation of gastrointestinal protein loss with $copper^{67}$-labeled ceruloplasmin, J. Clin. Invest., 44:1107, 1965.

24. Waldmann, T. A., and Schwab, P. J.: IgG (7S-gammaglobulin) metabolism in hypogammaglobulinemia: Studies in patients with defective synthesis, gastrointestinal protein loss, or both, J. Clin. Invest. 44:1523-1533, 1965.

25. Waldmann, T. A., Steinfeld, J. L., Dutcher, T. F., Davidson, J. D., and Gordon, R. S., Jr.: The role of the gastrointestinal system in "idopathic hypoproteinemia," Gastroenterology 41:197-207, 1961.



CASE REPORTS

Pneumococcal Pericarditis in An Eight-Month-Old Child

LAWRENCE MADOFF, M.D., *Oakland*

WITH THE WIDESPREAD use of antibiotics, particularly penicillin, reported cases of pneumococcal pericarditis in infants and children are rare. Benzing and Kaplin in 1963 reviewed seven cases of purulent pericarditis they had observed over a 10-year period, one of which was due to pneumococcus.[2] The following is a case report of an eight-month-old infant in which the diagnosis was not immediately considered, and a brief discussion of management and treatment.

Report of a Case

The patient was an American Indian boy born 10 April 1965. Delivery was normal and birth weight was eight pounds three ounces. He was apparently in good health until two weeks before his admission to Highland General Hospital, 1 January 1966. Illness had begun with cough and vomiting. Several days later the child began to have numerous loose bowel movements daily and a physician prescribed benylin expectorant and oxytetracycline (Terramycin®) syrup. The condition of the patient apparently improved and the diarrhea subsided for four or five days. Three days before admission to hospital, however, the patient began to vomit several times daily. The mother at this time noticed the onset of rapid breathing and fever. She gave the child aspirin, 60 mg (1 grain) two to three times daily for three days. The patient again was seen by a physician who made a diagnosis of dehydration and acidosis and had him admitted to Highland General Hospital.

Physical Findings

On admission, 1 January 1966, the patient appeared well developed and nourished, ill and lethargic but in no acute distress. Temperature was 39.4°C (103°F), respirations were 48 per minute and the pulse was 160 per minute and regular. There was some flaring of the alae nasae and grunting respirations. On examination of the chest the breath sounds were normal and no rales were heard. The heart sounds were normal. The abdomen was slightly distended and the edge of the liver, nonpulsatile, was palpable 1 cm below the right costal margin. Bowel sounds were active. Skin rubor was good. No other abnormalities were noted on physical examination.

Sodium content of the serum was 133 mEq, potassium 5.8 mEq and carbon dioxide 10.5 mEq per liter. No abnormality was noted in the cerebral spinal fluid. Leukocytes numbered 14,950 per cu mm of blood—42 per cent polymorphonuclear cells, 13 per cent band forms, 5 per cent metamyelocytes and 40 per cent lymphocytes. Urinalysis showed a slight trace of acetone and albumin, and on microscopic examination there were two to four leukocytes and four to six erythrocytes per high power field. An x-ray film of the chest was interpreted as within normal limits with the

---

From Department of Pediatrics, Highland General Hospital, Oakland.

Submitted 25 April 1966.

Reprint requests to: Department of Pediatrics, Highland General Hospital, 2701 14th Avenue, Oakland, California 94606 (Dr. Robert Cooper).

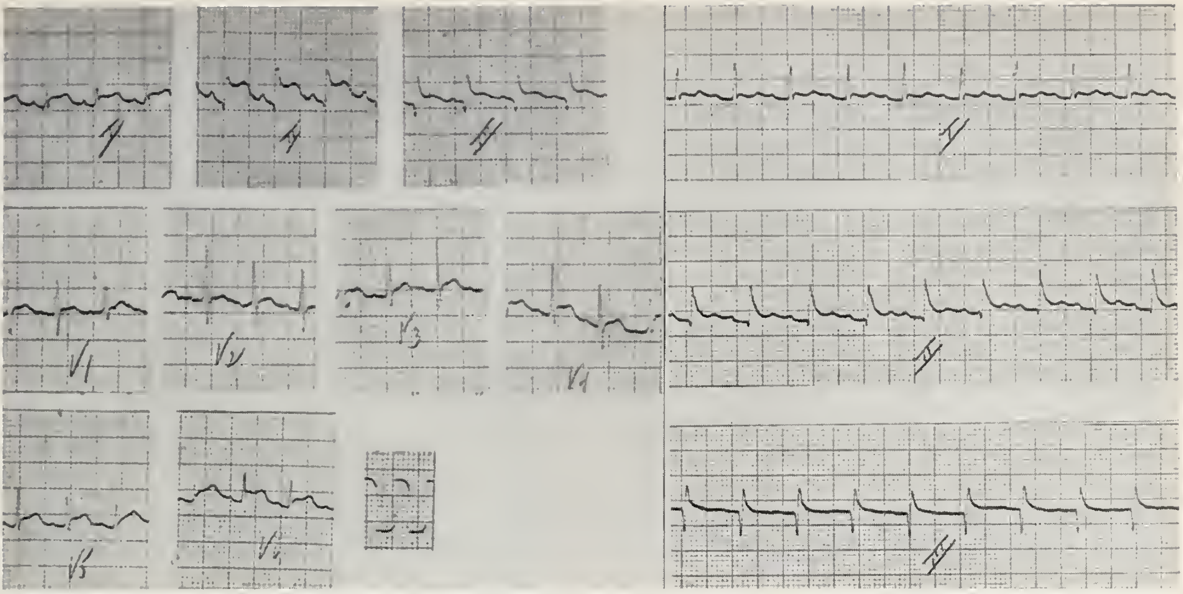


Figure 1.—*Left*, electrocardiogram taken 12 hours after admission showing ST elevation throughout chest leads. *Right*, electrocardiogram taken two hours after pericardiocentesis, showing lowering of ST segments.

heart size at the upper limits of normal. Blood was drawn for culture and sensitivity tests.

The initial impression was acidosis and mild salt and water depletion secondary to vomiting and diarrhea. Replacement and maintenance therapy with intravenous fluids was begun. Twelve hours after admission there was no improvement. The abdomen was more distended. The liver edge was now palpable 4 cm below the right costal margin. Grunting respirations and tachycardia continued. On auscultation of the chest, normal breath sounds were heard, without rales, and heart sounds were normal. No abnormality was noted on rectal examination. An electrocardiogram taken at this time showed ST elevation throughout the chest leads (Figure 1). The impression at that time was myocarditis and congestive heart failure secondary to sepsis. Administration of digoxin, penicillin and kanamycin was begun. During the next 12 hours the patient's condition worsened. Color was poor and respirations irregular and decreasing. Endotracheal intubation was carried out and respiration was assisted with positive pressure. Sodium bicarbonate solution was given intravenously with moderate improvement. After an hour of assisted respiration, the endotracheal tube was removed and the patient breathed spontaneously with improved color. X-ray films of the chest at this time showed infiltrations of both upper lobes and cardiomegaly (Figure 2). The following morning, 32 hours after admission, in consultation with members of the cardiology service, pericardiocentesis was performed through the base of the xyphoid process, although signs of tamponade were not present. On removal of 75 ml of thick, purulent material, the child's respiratory effort and color immediately improved. On auscultation a pericardial rub was clearly audible. A Gram-stained specimen of the aspirated fluid showed diplococci. Diplococcus pneumoniae grew on the blood culture taken on admission. Subsequently a culture of the aspirate grew the same organism.

In consultation with members of the thoracic surgery service, it was decided to continue medi-

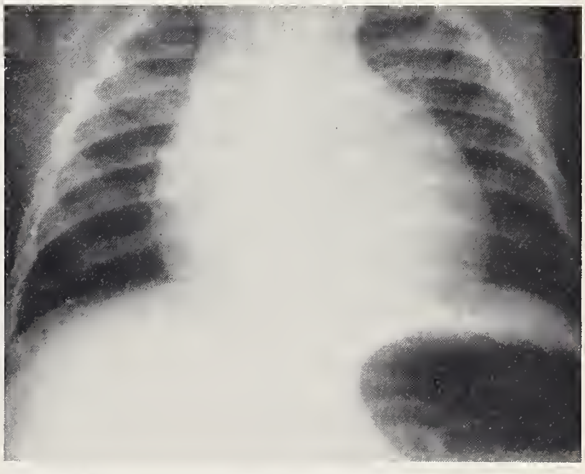


Figure 2.—Repeat chest film taken on second day in hospital, showing infiltrations of both upper lobes and cardiomegaly.

cal management and to perform pericardiocentesis as needed. Five million units of penicillin was given daily by vein. An electrocardiogram two hours after the first aspiration of fluid showed lowering of the ST segments (Figure 1). On the fifth hospital day grunting respirations returned and the pericardial rub was no longer audible. On aspiration carried out at that time 30 ml of cloudy, serous fluid was withdrawn. A polyethelene catheter was inserted into the pericardial sac through a No. 13 gauge (French) needle and the sac was irrigated with one million units of aqueous crystalline penicillin. The catheter was left in place and the procedure repeated the following day without return of fluid.

The patient continued to improve although the temperature remained elevated for 10 days. He was maintained on high doses of parenteral penicillin. On the seventeenth hospital day he was discharged completely recovered. Long acting penicillin was given intramuscularly on discharge. During four months of intermittent observation in the outpatient department the child remained well, and an x-ray film showed a moderate decrease in cardiac silhouette.

Comment

Reports in the literature suggest that pneumococcal pericarditis is a result of direct extension from a pneumonic process in the adjacent lung parenchyma.[3,5] It is generally recommended that surgical drainage is the therapy of choice in infants and children.[1,2,4] The patient in the present case was successfully treated with repeated pericardiocentesis and antibiotics alone. Diplococcus pneumoniae, the only organism cultured in the case here reported, is very susceptible to penicillin. However, if a resistant organism is present, surgical drainage would appear to be indicated in order to completely eliminate the offending organism from the pericardial cavity. As was illustrated in the present case, periocardiocentesis can be a useful diagnostic as well as a therapeutic procedure.

Summary

A case of pneumococcal pericarditis in an eight-month-old child is reported. The patient was successfully treated with antibiotics and periocardiocentesis.

REFERENCES

1. Ainger, L.: Acquired Heart Disease in Infants and Children in Brennemann: Practice of Pediatrics, 33; chapter 37, W. F. Prior Co., Hagerston, Md., 1962.

2. Benzing, G., III, and Kaplin, S.: Purulent pericarditis, Amer. J. Dis. Chld., 106:289, 1963.

3. Boyle, J. D., Pearce, M. L., Guzel, L. B.: Purulent pericarditis: Review of literature and report of 11 cases, Med., 40:119, 1961.

4. Crastnopol, P., Kroop, I. G., Levy, G.: Management of pericardial effusions by pericardiectomy, New York J. Med., 582:2367, July 1958.

5. Nadas, A. S., and Levy, J. M.: Pericarditis in children, Amer. J. Cardiol., 7:109, 1961.

Cystic Pulmonary Metastasis Complicating Angiosarcoma Of the Scalp

DOUGLAS W. CARDOZO, M.D., *Santa Rosa*; PHILLIPS L. CLAUD, M.D., AND IRENE CHEN, M.D., *El Centro*; AND ALFRED A. THURLOW, JR., M.D., *Santa Rosa*

ACCORDING TO FREILICH and Coe,[2] a review of the literature from 1918 to 1934 disclosed only 29 reported cases of angiosarcoma, some of which Kinkade[3] believed were not true angiosarcomas. Kinkade reviewed the literature from 1939 to 1949 and "after reading reports of 118 cases labeled with some name suggestive of a malignant vascular tumor," he felt compelled to reject 41 of them "either because there was an inadequate or no histological report, or because . . . the illustrations and texts described a tumor of some other kind." Although he pointed out that the true incidence of angiosarcoma is actually greater than reported, these tumors are not often encountered. The case here reported showed the unusual added features of cystic pulmonary metastasis and hemopneumothorax, demonstrated by x-ray study of the chest and confirmed by autopsy, and adds another possibility to the differential diagnosis of cystic disease of the lung.

Submitted 21 February 1966.

Reprint requests to: 50 Montgomery Drive, Santa Rosa, California 95404 (Dr. Cardozo).

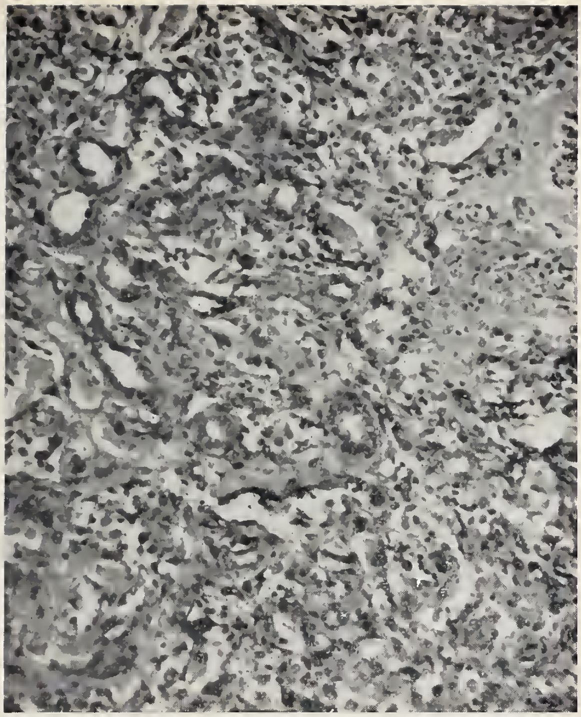


Figure 1.—Photomicrograph of the primary lesion in the scalp—angiosarcoma (×400).

Report of a Case

The patient, a 77-year-old Filipino agricultural laborer, already had two "pimples" on the scalp in April 1960 when he noted a lump on the right side of his head. Soon afterward another lump appeared on the scalp, this time on the left side. When the latter bled in July 1960, the patient consulted a physician. Biopsy (Figure 1) revealed numerous irregular, tortuous and anastomosing vascular channels (often lined by large endothelial cells), and the proliferation of endothelial cells, a few of which had large and deeply stained nuclei. A few mitotic figures were seen. The histologic diagnosis was "hemangioma of the scalp." The patient thereupon was referred to the surgical clinic of the University of California Medical Center at Los Angeles, and on 17 October another biopsy showed tumor cells with large pleomorphic nuclei and abundant cytoplasm scattered throughout the dermis, frequently forming vascular spaces. Several mitotic figures and a few tumor giant cells were present; some cells had spindle shaped nuclei. Many lymphocytes and neutrophils were seen in the dermis, as well as a few foreign body giant cells. The histologic diagnosis was "malignant vascular tumor, probably angiosarcoma." Upon review of the slides from the first biopsy, they were interpreted as suggestive of "angiosarcoma arising in hemangioma."

Physicians in the surgical clinic recommended excision to be followed by irradiation. The patient returned to his home and reported to the outpatient department of the Imperial County Hospital on 31 October 1960, with complaint of discomfort in the chest, hemoptysis and bleeding from the scalp.

On physical examination the patient appeared well developed and well nourished. He was of dark complexion and appeared younger than the stated age of 77 years. The temperature, pulse, respiration and blood pressure were within normal range. On the scalp there were five separate round tumors, each with the following characteristics: Raised indurated borders, soft central umbilication, a black crust with underlying spongy and bloody tissue, and an irregular margin of bluish-red discoloration about 1 cm wide. From the umbilicated center of the tumor above the left ear soft white tissue protruded. The tumor located in front of the left tragus covered the temporo-mandibular area, and an irregular bluish-red discoloration of the skin extended from it to the left eye. The two lesions on the right side of the scalp measured 2.5 cm and 3 cm in diameter, while those on the left were 2, 4, and 6 cm in diameter.

The hemoglobin was 8.2 gm per 100 ml of blood, hematocrit 28 per cent, leukocytes 17,000 per cu mm, with 85 per cent segmented neutrophils, 12 per cent lymphocytes, 2 per cent monocytes, and 1 per cent stabs. Urinalysis was normal and the Venereal Disease Research Laboratory test weakly reactive.

Unexpectedly, x-ray films showed a localized area of pneumothorax at the right costophrenic angle, and the right diaphragm was slightly elevated. A thin-walled cystic annular shadow (2.5 cm in diameter) was in the right apex, and another (3.0 cm in diameter) in the left base. On 10 November 1960 the patient was admitted to the Imperial County Hospital. Skeletal survey showed no abnormalities. Films of the chest now showed seven thin-walled cystic annular shadows in the right lung and two in the left lung. The coccidiodin test was negative, and the prothrombin time 100 per cent of normal.

Radiotherapy was administered and definite regression of the scalp lesions followed. On 29 November 1960 the patient was readmitted to the

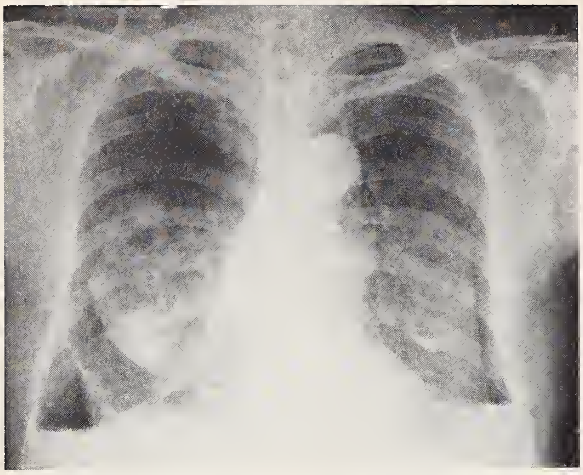


Figure 2.—Posteroanterior roentgenogram of the chest, showing bilateral hydropneumothorax and accentuation of cystic shadows. 29 November 1960.

hospital because of dyspnea and hemoptysis. An x-ray film of the chest (Figure 2) showed bilateral pneumothorax with 40 per cent collapse of each lung. The previously noted cystic shadows appeared accentuated, and at least six cysts were seen in the partially collapsed left lung, the largest being the earliest one detected (October 1960) which now was 4.5 cm in diameter. Pneumothorax was treated by the insertion of large polyethylene tubes into each pleural cavity through the second anterior intercostal spaces, and application of continuous suction. As air and bloody fluid were aspirated, the patient's condition improved dramatically. However, pneumothorax recurred intermittently and the areas of cystic rarefaction appeared to have increased in number bilaterally. A cell block made of the clotted bloody expectoration was reported as negative for tumor cells. The patient's condition became progressively worse, and he died 20 December 1960.

At autopsy multiple lesions consisting of gray-tan granulation-like tissue, surrounded by moth-eaten, mottled, green-brown margins, were seen on the scalp. The right pleural space contained a small amount of bloody fluid and free air. Both lungs were studded with innumerable hemorrhagic cysts that were a few millimeters to 18 millimeters in diameter. The cysts often contained blood or dark brown fluid but were largely air-filled. On microscopic examination of the scalp specimens many, often collapsed, anastomosing channels and capillaries were seen in the dermis and subcutaneous fat. These were lined by atrophic endothelial cells and separated by deposits of hyalinized collagenous connective tissue. A few neoplastic cells possessing irregular, large and hyperchromatic nuclei, and also a few multi-nucleated giant cells were present, as well as many hemosiderin-laden macrophages. In one section, however, the subcutaneous fat was infiltrated by numerous irregular large anastomosing channels lined by anaplastic endothelial cells, which possessed large spindle or irregular and deeply stained nuclei with a scant amount of cytoplasm and long cytoplasmic processes. Many bizarre and giant nuclei were also seen. From multiple sections of the lung it was determined that the cystic lesions were metastatic, since histologic examination of their walls showed the same angiosarcomatous structure as was found in the scalp lesions (Figure 3). In some areas, however, the pulmonary metastases appeared more anaplastic and cellular than the primary focus. The lumina of the cysts often contained blood or partially organized blood clots. Small arteries and veins were invaded by tumor, and "tumor emboli" were seen in the pulmonary vessels.

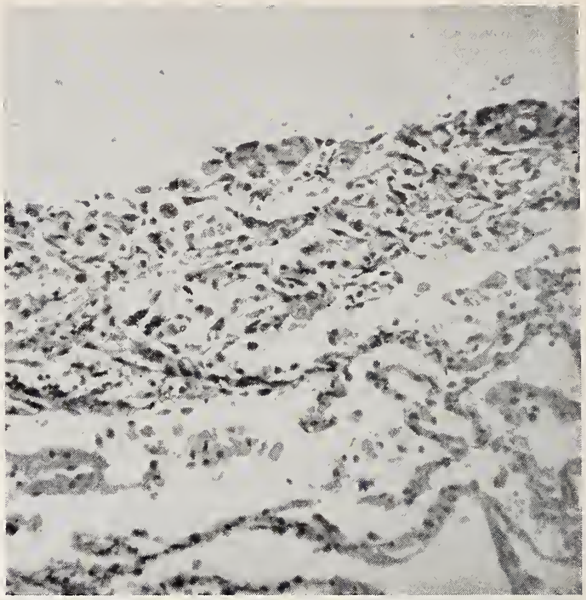


Figure 3.—Photomicrograph showing angiosarcomatous tissue forming the lining and wall of a pulmonary cyst (×400).

The anatomic diagnoses were:

1. Angiosarcoma, extensive, of scalp (previous biopsy excision and radiation therapy).

2. Metastatic angiosarcoma of both lungs with:

a. Tumor embolization of pulmonary vessels.

b. Invasion of blood vessels and pulmonary parenchyma.

c. Hemopneumothorax, right, secondary to rupture of hemorrhagic cystic metastasis.

Discussion

Several instances of angiosarcomatous pulmonary metastases have been reported.* In five of six cases of angiosarcoma of the breast reported by McClanahan and Hogg,[8] pulmonary metastasis developed—"hemoptysis was almost a constant feature late in the disease and usually appeared before the roentgenograms confirmed pulmonary metastases." Their review also summarized nine reported cases of angiosarcoma of the breast. In six, spread to the lung were demonstrated. In the second of two cases of angiosarcoma of the liver described by Bloch[1] there were pulmonary lesions described as numerous, scattered, circular areas up to 0.5 cm in diameter, composed of "a white center surrounded by a hemorrhagic rim. . . . In the lungs the tumor nodules were limited to the thickened pleura and septa." A case of primary angiosarcoma of the pleura with repeated accumulation of bloody pleural effusion was reported by Stout.[13] Lorber[5] described a three-year-old girl with hematuria in whom miliary pulmonary opacities developed and later became coarser. At autopsy "the lungs were studded throughout with a multitude of small hemorrhagic nodules 0.1 to 1.0 cm in diameter." Microscopic sections of the nodules were cavernous and many of the spaces were filled with blood or proliferating endothelial cells. Lane[4] reported the case of a 69-year-old woman with angiosarcoma of the face and scalp, and autopsy revealed "numerous discrete, firm, red spherical nodules (up to 3.0 cm in diameter)" in the substance of both lungs. These nodules revealed "vascular spaces lined by a single layer of endothelium and filled with erythrocytes and blood clot. In parts the spaces roughly conform to the shape of the alveoli by whose walls they are supported. . . . In other places both alveolar walls and the walls of the vascular spaces have broken down, so that there is variation in size and shape of the spaces, and at the periphery the edge is indefinite and blood seeps into the adjacent alveoli." Lane[4] and Tibbs[15] demonstrated tumor tissue in the lumen of pulmonary vessels. Lane concluded that the lesions in the cervical nodes and lung were embolic. In the second of the two cases reported by Bloch[1] in 1958, as well as in the present case, angiosarcomatous tissue was seen invading the walls of pulmonary vessels in the lung. Stout[13] considered spread and infiltration as occurring by "a process similar to the formation of capillaries in granulation tissue" which is manifested by "sprouting of endothelial cells from pre-existing capillaries, forming first a solid cord which secondarily becomes canalized." The frequency of hemotogenous spread was also alluded to by Stout.[13]

In the present case it would have been interesting to study a film of the chest taken before the appearance of the lesions in the scalp, but none had been taken. Nonetheless, it is logical to assume that the pulmonary lesions were secondary deposits arising by embolic spread from the primary process in the scalp, even though the lung lesions showed more pronounced anaplasia and cellularity than the primary site. This disparity has been noted by others.[6,9,11,14] This case satisfies the criteria mentioned by Stout[13] as being essential for the diagnosis of malignant vascular tumors, the constant features of which are: "(1) The formation of atypical endothelial cells in greater number than are required to line the vessels with a simple endothelial membrane, and (2) The formation of vascular tubes with a delicate framework of reticular fibers and a marked tendency of their lumens to anastomose." In addition to these features, actual invasion of the pulmonary vessels was demonstrated as well as embolization of tumor tissue into the vessels of the lungs.

Summary

A case of angiosarcoma of the scalp with the development of unusual cystic metastasis in both lungs has been presented.

Subsequent rupture of these cysts caused bilateral hemopneumothorax as shown by serial x-ray films of the chest.

REFERENCES

1. Bloch, C.: Malignant hemangioendothelioma. Report of two cases and review of literature, J. Mt. Sinai Hosp., N.Y., 25:115-127, March-April 1958.

2. Freilich, E. B., Coe, G. C.: Angiosarcoma: Case report and review of the literature, Am. J. Cancer, 26: 269, February 1936.

3. Kinkade, J. M.: Angiosarcoma: A review of the literature, Ann. Otol. Rhin. & Laryng., 58:159, 1949.

4. Lane, O. G.: Cutaneous angiosarcoma with metastases, Brit. J. Cancer, 6:230-235, 1952.

5. Lorber, J., Ackerley, O. G.: Malignant hemangioendotheliomata simulating miliary tuberculosis and neu-

---

*Reference Nos. 1, 2, 5, 7, 8, 10, 12, 13, 15.

roblastoma of the adrenal, Proc. Roy. Soc. M. London, 51:288-290, April 1958.

6. Mallory, F. B.: The results of the application of special histological methods to the study of tumors, J. Exp. Med., 10:575, 1908.

7. McCarthy, W. D., Pack, G. T.: Malignant blood vessel tumors—Report of 56 cases of angiosarcoma and Kaposi's sarcoma, Surg. Gynec. & Obst., 91:465, 1950.

8. McClanahan, B. J., Hogg, Lewis, Jr.: Angiosarcoma of the breast, Cancer, 7:586, 1954.

9. Hansom, H. K., Samson, P. C.: Malignant tumors of the greater omentum, Ann. Surg., 100:523, 1934.

10. Raven, R. W., Christie, A. C.: Hemangiosarcoma—A case with lymphatic and hematogenous metastases, Brit. J. Surg. XLI, 169:483-489, March 1954.

11. Robinson, J. M., Castelman, B.: Benign metastasizing hemangioma, Ann. Surg., 104:453.

12. Shore, J. H.: Hemangiosarcoma of the breast, J. Path. & Bact. LXXIV, 2:289, 1957.

13. Stout, A. P.: Hemangioendothelioma—A tumor of blood vessels featuring vascular endothelial cells, Ann. Surg., 118:445-464, 1943.

14. Theile: Virchows Arch, 178:296, 1904.

15. Tibbs, D.: Metastasizing hemangiomata—A case of malignant hemangioendothelioma of the breast, Brit. J. Surgery, 40:465-470.

Progressive Pulmonary Insufficiency Due to Mineral Oil

ROBERT S. EISENBERG, M.D.
AND
WILLIAM H. OATWAY, JR., M.D., *Altadena*

CHRONIC aspiration pneumonitis due to lipids has been well studied in the past from a clinical standpoint. However, this entity is occasionally still with us, and particular attention must be paid to distinguishing the advanced form of this disease from other types of chronic obstructive airway disease with similar pulmonary function findings.

Mineral oil pneumonia in humans was first described in the literature by Laughlen[10] in 1925. In the next decade, the articles were chiefly concerned with case reports in children and with experimental work. In 1937, Ikeda[8] reviewed the literature and summarized 106 cases of lipoid pneumonia, more than half of which involved children. In 1943 Sweeney[17] made a further review of 264 cases, and subsequent reports[15] indicated no apparent diminution in incidence. In 1951, Volk and coworkers[18] randomly surveyed 389 chronically ill patients in one institution and found evidence in the sputum or in lung aspirate of lipoid pneumonia in 14.6 per cent of them. These findings resulted in warnings against the use of nose-drops containing oil and the use of such agents was quickly discontinued. There are other sources of oil inhalation, and a residue of people who once used oil nose-drops still exists.

It has been only recently that physiological data have been accumulated in an attempt to delve into the mechanism of the deleterious effects of mineral oil pneumonia. Weill and coworkers,[19] in 1964, reported a 38-year-old service-station attendant with acute lipoid pneumonia from nose-drops who showed significant reduction of lung volume without airway obstruction on pulmonary function testing. Also, arterial oxygen desaturation was present after exercise, along with uneven distribution of inspired air, suggesting a ventilation-perfusion abnormality. A more advanced case of lipoid pneumonia due to mineral oil was reported by Miller and coworkers[13] in a 55-year-old white man with a history of dust exposure and pulmonary disease for at least eight years. The sputum contained fat macrophages, and the patient was partially disabled. Pulmonary function testing in this patient showed obstructive airway disease as evidenced by a decidedly impaired maximum breathing capacity, in addition to restrictive involvement and a more severe ventilation-perfusion disturbance.

The following case is an example of the final result of the progression of mineral oil pneumonia.

Report of a Case

An 86-year-old white man entered La Vina Sanatorium and Hospital Respiratory Disease Unit on 30 June 1964, with complaint of severe shortness of breath and fatigue. He had been well until, three years before admission, he had a bout of pneumonia. Following this, he noticed shortness of breath and a dry cough. This condition responded to treatment and the patient became asymptomatic.

In the year before his admission, he began to have pronounced fatigue and dyspnea, and for eight months before admission these symptoms

---

From the Respiratory Disease Unit of La Vina Sanatorium and Hospital, Altadena, and the Department of Medicine, University of Southern California Medical School, Los Angeles.

Supported in part by a grant from the Pasadena Tuberculosis Association.

Submitted 3 May 1966.

Reprint requests to: La Vina Sanatorium and Hospital, La Vina Station, Altadena, California 91001 (Dr. Oatway).

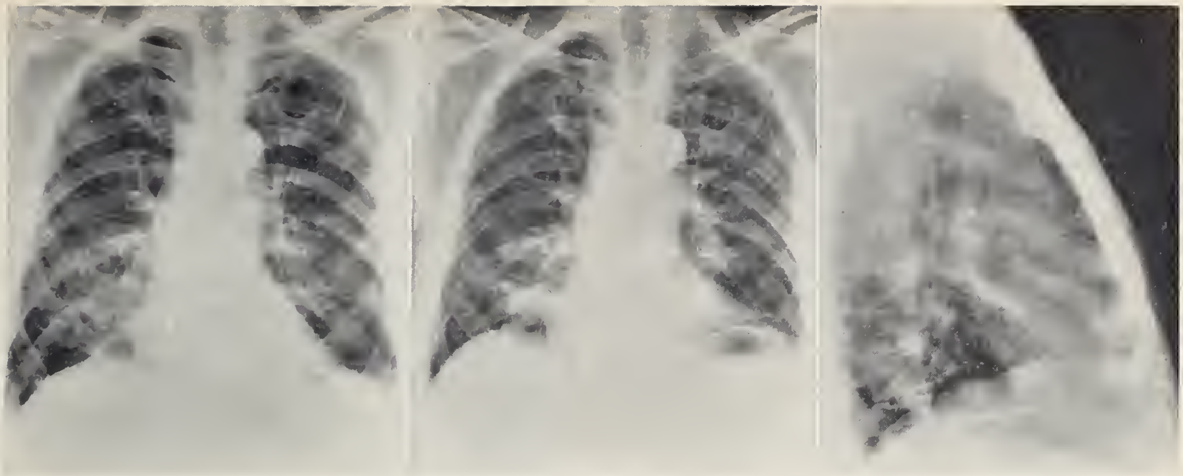


Figure 1.—Films taken on admission. *Left*, on inspiration; *center*, taken at full expiration; *right*, lateral.

were relieved only by an Emerson intermittent positive pressure breathing (IPPB) apparatus and by intravenous aminophyllin. The patient smoked cigars and cigarettes until four years before admission, when he stopped. He was also known to have ingested large quantities of mineral oil for constipation in the past three years, sometimes as much as a quart a day.

On physical examination, the patient was found to be quite tan but also very cyanotic. He was dyspneic after getting up and walking to the bedside commode but he was able to lie down comfortably flat in bed. Blood pressure was 150/80 mm of mercury, the pulse rate 86 and regular, and respirations 26 per minute. On examination of the thorax decreased mobility of the diaphragms and hyperexpansion of the chest wall were noted. Breath sounds were decreased bilaterally and no rales or rhonchi were present. The patient made use of accessory muscles of respiration to assist breathing. No cardiac abnormalities, other than an accentuated pulmonic second sound, were noted. There was slight cyanosis of the nail beds but no clubbing or edema was present.

X-ray films of the chest on admission showed bilateral unresolved pneumonia, cystic emphysema, cor pulmonale, advanced osteoporosis of the thoracic vertebrae with osteoarthritic lipping, and a fusion of the first and second rib on the right (Figure 1). Results of later x-ray studies were as follows: 19 August 1964—some decrease in size of the giant cysts, but the heart essentially unchanged; 3 November 1964, clearing and contraction of the large patch beneath the right hilus; 23 February 1965, cystic areas essentially unchanged in the upper and lateral right lung, and pulmonary fibrosis on the right in the midlobe location (Figure 2).

Laboratory findings included: Hematocrit, 48 per cent; hemoglobin, 15.85 gm per 100 ml; sedimentation rate, 3 mm in one hour; leukocytes, 9,500 per cu mm with cell differential within normal range. Results of urinalysis were normal. Sputum analysis for lipoid containing macrophages by the method of Volk and coworkers[18] was negative on two occasions. On 5 April 1965 serum vitamin A level was 20 mg per 100 ml (normal

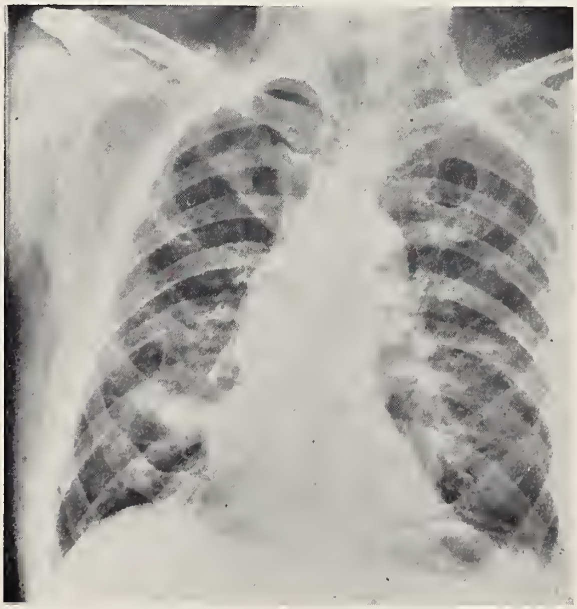


Figure 2.—Film of chest taken seven and one-half months after those in Figure 1.

TABLE 1.—*Results of Spirometric Determinations*

Test (in liters)	*3 July 1964 Without Aerosol*	*Isoproterenol Via Aerosol*	*21 Aug. 1964*
Inspiratory Vital Capacity	2.3 L (68%)	2.9 L (85%)	2.5 (72%)
Forced Expiratory Volume—1 sec.*	48%	45%	44%
Forced Expiratory Volume—3 sec.*	78%	69%	76%
Maximum Voluntary Ventilation	39 L/min. (45%)	42 L/min. (48%)	Unable

Spirometry done on 13.5 L Collins, and normals taken from Baldwin and coworkers[2] and Armstrong.[1] All values corrected to body temperature, ambient pressure and saturated.

*Forced Expiratory Volume Expressed as Per Cent of Total Forced Expiratory Volume.

20-60 mcg) and serum carotene was 120 mcg (normal 100-225 mcg). Results of pulmonary function studies are listed in Table 1 and Table 2.

Hospital Course

The patient was treated with bed-rest, IPPB, bronchodilators, forced fluids, antibiotics (according to sputum culture) and expectorants, all with minimal relief of shortness of breath. An electrocardiogram shortly after admission showed only a vertical axis. Serial electrocardiograms indicated progressive rightward deviation of the P-vector in the frontal plane and progressive posterior swinging of the QRS-vector in the horizontal plane, compatible with severe, chronic lung disease. In October 1964, administration of Lipo-Hepin® heparin sodium injection (USP), twice a day was begun in light reports of beneficial results of heparin in emphysema. No objective relief from this regime was observed and heparin was discontinued after a month. In December 1964 the patient complained of photophobia and aching in his eyes, unrelated to light. An ophthalmologist who was consulted believed that the symptoms were due to corneal endothelial dystrophy with senile, colloidal macular degeneration. These changes were attributed to vascular deterioration and not to vitamin A deficiency.

The patient's breathing became progressively worse and by the early portion of 1965, he was unable to get out of bed because of severe dyspnea. He required nasal oxygen for 24 hours a day, interspersed with intermittent positive pressure breathing every four hours. On 9 April 1965 he became semicomatose and unresponsive. Arterial blood gas studies done that day showed pH of 7.48, carbon dioxide pressure 39 mm of mercury, and oxygen saturation of 80 per cent (not changed from the past). Steroid therapy was begun, along with intensive antibiotic therapy and higher levels of oxygen. On 13 April the pH was 7.21, the oxygen pressure (with oxygen by nasal catheter at 11 liters per minute) was 86 mm of mercury and oxygen saturation was 90 per cent. Serum bicarbonate at that time was 29 mEq and potassium 4.8 mEq per liter. Pseudomonas was cultured from the sputum whereupon colymycin was discontinued and administration of chloramphenicol was begun. The condition of the patient continued critical and he died on 25 May 1965.

TABLE 2.—*Results of Arterial Blood Determinations*

Test	*26 September 1964*		*8 February 1965*	*9 April 1965*	*13 April 1965*
	At Rest	*Breathing 100 Per Cent Oxygen*		*At Rest*	
pH	7.35	7.44	......	7.48	7.21
H^+ concentration (millimoles per liter)	44.67	36.31	......	33.11	....
pO_2 mm Hg	50	460	......	41	....
pCO_2 mm Hg	36	34	42*	39	....
O_2 saturation	81 per cent	100 per cent	......	78 per cent	....
Plasma Bicarbonate mEq/L	19.8	23.2	......	29.4	....
Standard Bicarbonate mEq/L	19.8	23.2	......	29.4	....
Packed Cell Volume	48 per cent	....	......	58 per cent	....
Buffer Base	42.61	48.14	......	53.17	....
Alveolar-Arterial Gradient mm	52.6	177.63	......	61.6	....
Shunt	9.9 per cent	....	......	....	....

Radiometer Model 27 pH meter used with direct pO_2 electrode type E 5030, pCO_2 electrode, pHA 927 and gas monitor D-619.

*Rebreathing pCO_2 via Hackney Apparatus.

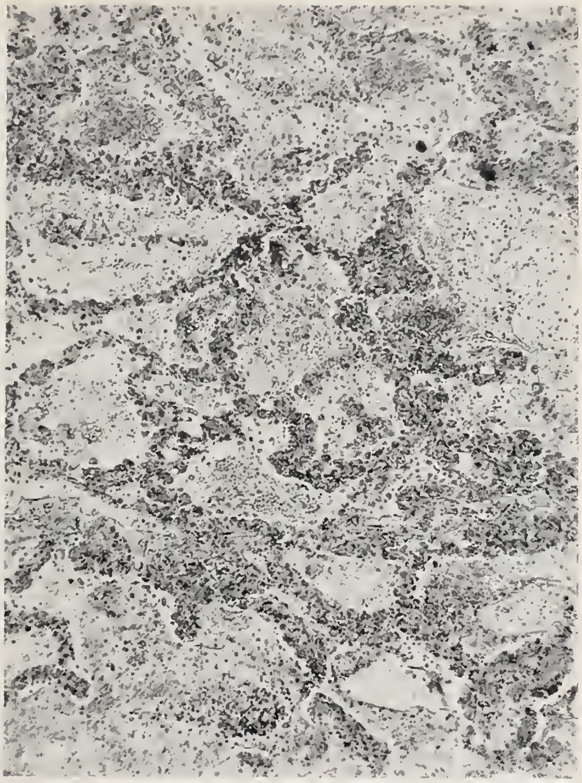


Figure 3.—Photomicrograph of lung of fatal lipoid pneumonia (×400).

Autopsy

Pertinent autopsy findings were as follows: The heart weighed 450 gm and right ventricle was 10 mm thick, the left ventricle 18 mm thick. The valves showed a mild thickening and the circumference of the rings was as follows: Mitral 11 cm; aortic 10 cm; pulmonic 10 cm; tricuspid 16 cm. The coronary arteries showed mild atherosclerosis and narrowing, but the lumens were patent everywhere.

The lungs were voluminous and decidedly emphysematous with bullae and blebs measuring from one to seven cm in diameter. The left lung weighed 600 gm and the right 650 gm. Sections through the hila showed some fibrosis and honeycombing but fatty material did not exude grossly from the surfaces. The microscopic section, however, showed multinucleated foreign body giant cells with large vacuoles (Figure 3). Diffuse fibrosis was also present, with destruction of the normal air spaces. Fat stains showed the vacuoles to be Sudan-positive (Figure 4).

Autopsy diagnoses: Lipoid pneumonia (mineral oil), chronic, severe bronchopneumonia; pronounced pulmonary emphysema and fibrosis; severe chronic bronchitis and bronchiolitis; decided right ventricular cardiac hypertrophy and dilatation (cor pulmonale).

Interpretation of Pulmonary Function Testing. The decrease in the maximum voluntary ventilation, the one- and three-second forced expiratory volumes, and the vital capacity (Table 1) were felt to be due to both obstructive airway disease and the loss of total ventilable lung. This was slightly improved by bronchodilators.

Arterial blood gas studies (Table 2) showed both hypoxemia and arterial desaturation which rose to near-predicted value with 100 per cent oxygen inhalation. This was felt to be due to physiologic shunting, most likely secondary to a disturbance in the normal ventilation-perfusion ratio of the lung. Because of the patient's severe dyspnea, it was not possible to do further studies.

Discussion

Despite the fact that the diagnosis of mineral oil pneumonia was not definitely made antemortem, it was strongly suspected because of (1) the long history of using mineral oil, (2) the large amounts of oil that were used and (3) the age

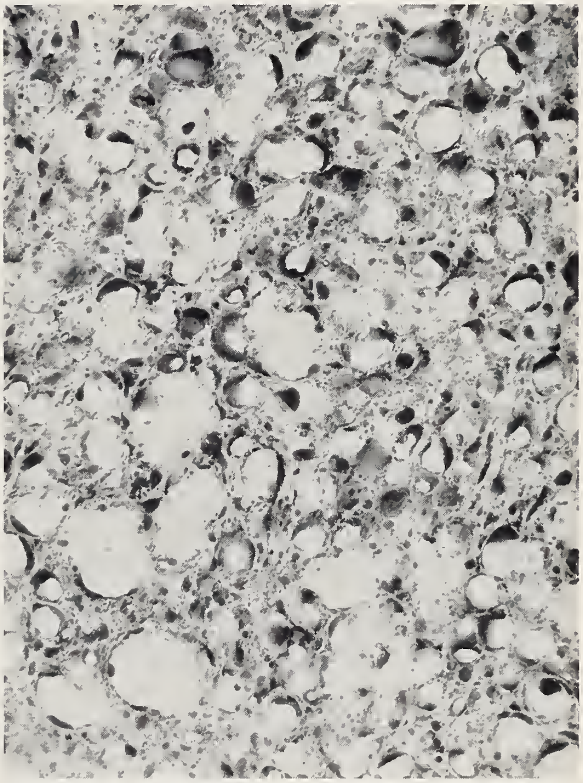


Figure 4.—Photomicrograph showing Sudan-positive vacuoles present within alveoli (×400).

of the patient at the onset of respiratory disease. Because of the patient's critically ill state, it was furthermore felt that transthoracic lung aspiration as a diagnostic procedure for lipoid pneumonia (as has been done in the past[18]) should not be done in this case. The ophthalmologic findings were felt to represent arteriosclerotic vascular changes. It would be of further interest to speculate whether or not the same cerebral vascular changes might have been responsible for both the inactivity of the bowels and cough reflex. Most investigators agree, however, that mineral oil is bland and nonirritating, and furthermore is capable of entering the lung from the pharynx with little or no cough reflex. Quinn and Meyer[14] demonstrated many years ago that iodized oil which was instilled into the pharynx during the night could be found by x-ray in the posterior lung bases the following morning.

One may conjecture as follows upon a possible migration of mineral oil taken at bed-time: Since it is lighter than gastric or abdominal contents, it will float. Since average pressure within the stomach is positive, and within the thorax is negative, the globules of mineral oil may be regurgitated up the esophagus into the pharynx. The oil also interferes with ciliary activity and could be easily aspirated by a sleeping person, settling into the most dependent portion of the lung.

Pathologic Features of Mineral Oil Pneumonitis. Most cases of lipoid pneumonia are asymptomatic and are diagnosed only at necropsy.[3] The symptomatic types can be further classified—one kind is circumscribed granuloma which may roentgenographically resemble cancer, the other is diffuse mineral oil granuloma.[11] The exact type of lung response to a given oil depends on (1) viscosity, (2) surface tension, (3) amount, (4) chemical construction.[5] For example, mineral oil does not characteristically cause the severe, acute pulmonary edema and hemorrhage that kerosene or similar low-viscosity mixtures cause. Mineral oil is a saturated alkyl carbon chain which does not undergo metabolic changes in the body[12]; thus, assimilation and absorption are impossible. Ultimately there is a foreign-body granulomatous reaction with slow development of fibrotic tissue. Occasionally some mineral oil is carried by macrophages to adjoining lymphatic structures, and even more rarely emboli may be carried to other parts of the body such as the spleen.[6] Since mineral oil is Sudanophilic, it may be distinguished from vegetable and animal oils by its failure, in most cases, to reduce osmic acid. Its capacity to absorb other materials, such as mucous steroids and organic fats, may make differential staining difficult. In such instances it may be necessary to boil the specimen in sulfuric acid or to carry out chemical analysis of material extracted with fat solvents.[9]

Roentgenographic Features. Roentgenographic findings are most commonly those of either a localized granuloma or extensive bilateral basal unresolved infiltrate.[20] Weill and coworkers[19] emphasized the occurrence in lipoid pneumonia of an "acinar pattern" composed of many rosettes 6 mm or less in diameter. They expressed the belief that identification of acini or primary lobules permits distinguishing this process from other pulmonary infiltrates in which the supporting tissue is primarily involved with the obliteration of the air sacs. Acinus filling, when found, would suggest aspiration pneumonitis, pulmonary hemosiderosis, pulmonary alveolar proteinosis, acinous-nodose tuberculosis or pulmonary edema.

Clinical-Physiologic Features. The physiological findings in the present case suggested a ventilation perfusion abnormality which became progressively worse, eventually terminating in acidosis. In addition, obstructive airway disease was also present and it did not significantly improve with bronchodilators. This condition is probably a result of peribronchiolar and peribronchial fibrosis,[7] in addition to chronic bronchial inflammation. It is also not unreasonable to assume that the pulmonary perivascular fibrosis in the present case was extensive enough to result in pulmonary hypertension and cor pulmonale, as evidenced by the autopsy findings. The postmortem association of chronic mineral oil pneumonitis and chronic cor pulmonale in a patient without arterial desaturation has been noted in the past.[4]

Treatment. The treatment of progressive pulmonary insufficiency due to mineral oil consists of general supportive measures and immediate discontinuance of the use of mineral oil. Supportive measures include the use of oxygen to correct hypoxemia, of antibiotics to treat intercurrent respiratory infections, and of bronchodilators and expectorants. In addition, digitalis, diuretics and salt restriction are necessary if cor pulmonale is present. The role of steroids has not yet been adequately evaluated but may be beneficial. Prophylactic treatment would include (1) not using mineral oil as a lubricant for nasogastric tubes or esophageal bougies,[16] (2) not using mentholated petroleum jelly or oil nose drops in upper respiratory passages, (3) not using mineral oil in elderly people either as a laxative or to combat lip dryness.

Summary

A case of mineral oil-induced pulmonary insufficiency, eventually terminating in respiratory acidosis and death, is presented. Particular emphasis is placed on the physiological findings and the pathogenesis of this condition because of the overt resemblance of this disease to other types of progressive, chronic obstructive airway disease. Prompt diagnosis and immediate discontinuance of mineral oil are the most effective management.

GENERIC AND TRADE NAME OF DRUG
Heparin sodium injection (U.S.P.)—*Lipo-Hepin.*

REFERENCES

1. Armstrong, Bruce W.: Nomograms of normal males and females, Pulmonary Function Department, University of Southern California Medical School.

2. Baldwin, E. Cournand, and Richards, D. W., Jr.: Pulmonary insufficiency, physiological classification, clinical methods of analysis, standard values in normal subjects, Medicine, 27:243, 1958.

3. Cannon, P. R.: Problem of lipoid pneumonia, J.A.M.A., 115:2176-79, 21 December 1940.

4. Casey, James F.: Chronic cor pulmonale associated with lipoid pneumonia, J.A.M.A., 177:896-898.

5. Gerarde, H. W.: Toxicological studies of hydrocarbons, Arch. of Environmental Health, 6:329-341, March 1963.

6. Greenridge, H. W., and Tuttle, M. D.: Lipoid pneumonia in a Veterans' hospital, Ann. of Int. Med., 43: 1259-1268, December 1954.

7. Guidey, L. D., Clagett, O. T., McDonald, J. R., and Kincaid, W. O.: Pulmonary resection for mineral oil granulomas, Ann. Surg., 150:67, 1959.

8. Ikeda, K.: Lipoid pneumonia of the adult type, Arch. Path., 23:470, 1937.

9. Jampolis, R. W., McDonald, J. R., and Clagett, O. T.: Mineral oil granulomas of the lungs: An evaluation of methods for identification of mineral oil in tissue, Surgery, Gynecology and Obstetrics, 97:105-119.

10. Laughlen, G. F.: Studies on pneumonia following naso-pharyngeal injections of oil, Am. J. Path., 1:407-414, July 1925.

11. McDonald, J. R., and Hodgson, C. H.: The problem of lipoid pneumonia or granuloma of the lung, Med. Clinics of No. Amer., 989-996, July 1954.

12. Mason, James M.: Lipoid pneumonia, adult type, Ann. of Surg., 141:940-943.

13. Miller, A., Bader, R. A., Bader, J. D., Teirstein, A. S., and Selikoff, I. J.: Mineral oil pneumonia, Ann. Int. Med., 57:627-634.

14. Quinn, L. H., and Meyer, O. O.: Relationship of sinusitis and bronchiectasis, Arch. Otolaryngology, 10: 152-165, 1929.

15. Sodeman, W. A., and Stewart, M. M.: Lipoid pneumonia in adults, Ann. Int. Med., 24:241, 1946.

16. Steinberg, I., and Finby, N.: Lipoid pneumonia and cor pulmonale due to cardiospasm, Am. J. Roentgenology, Radium Therapy and Nuclear Medicine, 76: 108-114.

17. Sweeney, W. J.: Intranasal medication with oils, Eye, Ear, Nose Monthly, 22:335, 1943.

18. Volk, B. W., Nathanson, L., Losner, S., Slade, W. R., and Jacobie, M.: Incidence of lipoid pneumonia in a survey of 389 chronically ill patients, Am. J. Med., 10:316, 1951.

19. Weill, H., Ferrans, V. J., Gay, R. M., and Ziskind, M. M.: Early lipoid pneumonia, Am. J. Med., 36: 370-376.

20. Wright, G.W., and Filley, G. F.: Pulmonary fibrosis and respiratory function, Am. J. Med., 10:642, 1951.

Intraperitoneal Migration Of a Kirschner Wire:

Report of a Case

EUGENE C. WEINSTEIN, M.D., TAKESHI HAYASHIDA, M.D., P. L. CLARK, III, M.D., AND ALICE L. GARRETT, M.D., *Downey*

ORTHOPEDIC SURGEONS FREQUENTLY use metallic pins for fixation and reports of migration of wires or pins used in fixation procedures have appeared periodically in the medical literature.[1,6] In the reported cases the areas involved were parts of the body that are subject to repeated motion, such as the shoulder and hip. In only one of the cases reported was the wire of the threaded variety.

In one instance at Rancho Los Amigos Hospital, a Los Angeles County Hospital at which the major interest is corrective and restorative orthopedic surgery, a metallic fixation device migrated into the peritoneal cavity.

Report of a Case

A Caucasian girl, when born at term, 13 September 1961, was immediately noted to have multiple congenital defects, in addition to arthrogryposis multiplex congenita. The major congenital abnormalities were agenesis of the third, fourth and fifth lumbar vertebrae and the sacrum, a cloaca, paraplegia and bilateral hip dislocation.

Submitted 2 March 1966.

Surgical and Orthopedic Services, Rancho Los Amigos Hospital, Downey.

Reprint requests to: 17050 Chatsworth Street, Granada Hills, California (Dr. Weinstein).

On 1 November 1963, open reduction of the dislocated left hip and subcutaneous adductor tenotomy were carried out. On 29 May 1964, acetabuloplasty of the left hip, utilizing two Kirschner wires, was done (Figure 1). Almost a year later a soft-tissue release of a flexion contracture of the left knee was done, and with it a lengthening of the heel-cord.

On 26 August 1965 routine x-ray films of the hip disclosed the migration of one of the Kirschner wires into the abdominal cavity (Figure 2). At this time the child had no complaints referable to the abdomen. On 3 September 1965 the abdomen was opened and a Kirschner wire which had migrated through the root of the mesentery and into the liver was removed without incident. Convalescence was rapid and the child was dismissed from the surgical service 10 September 1965.

Discussion

Two points of interest in the present case were that no other case could be found in the literature in which a pin migrated into the liver, and that the pin migrated through the root of the mesentery without perforation or vascular compromise of the intestine.

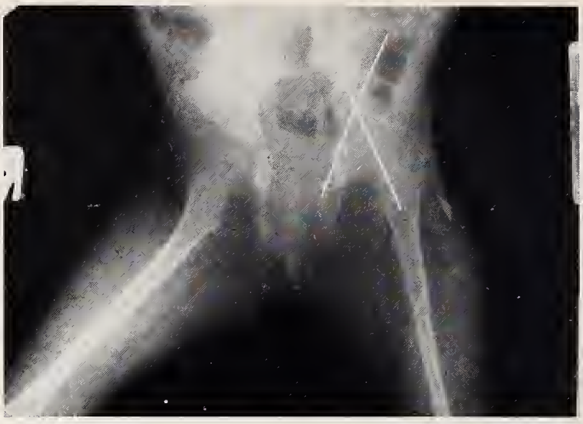


Figure 1.—Postoperative film showing two Kirschner wires in position after an acetabuloplasty of the left hip.

The usual explanation for migration of orthopedic fixation devices is regional resorption of bone, which allows the foreign body to respond to gravitational force or to the force created by normal activities of the body.

Kremens and Glauser[2] expressed belief that the migration of pins or wires from a site within the proximal portion of the clavicle or region of the sternoclavicular joint into the chest cavity was most probably due to the constant movement in respiratory excursion. As regards fractures of the middle or distal third of the clavicle, they believed

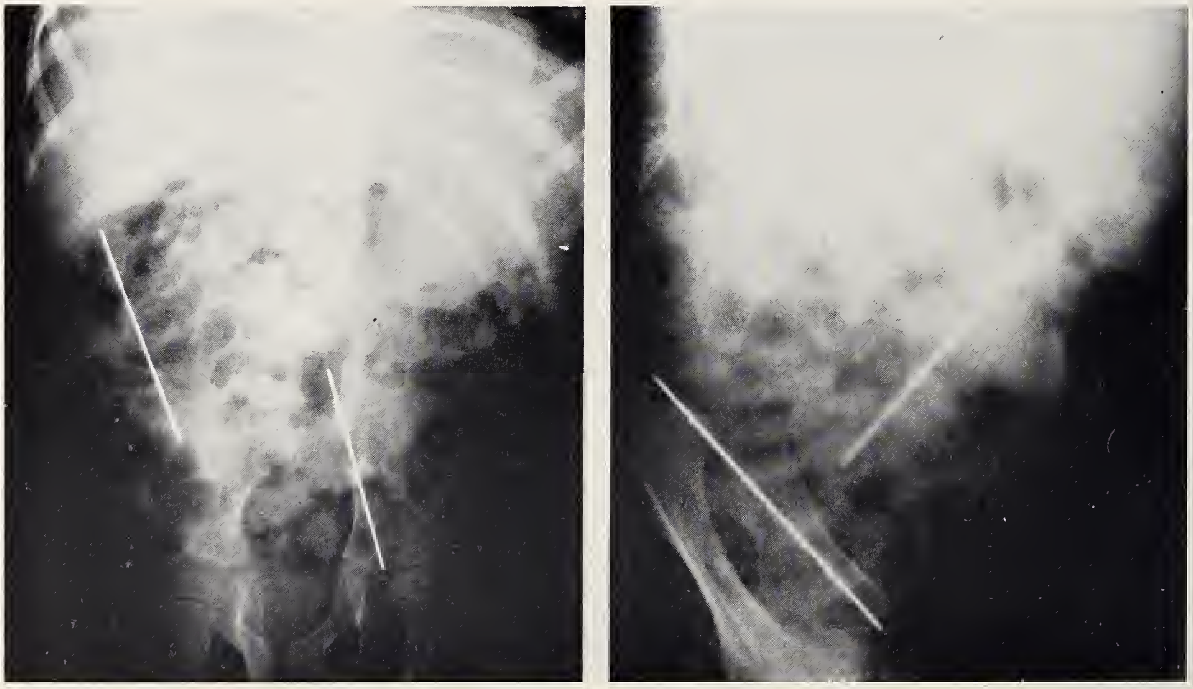


Figure 2.—In anterioposterior and lateral views, the presence of one Kirschner wire in the right upper quadrant is readily apparent. The left hip is still dislocated.

that migration was induced by movement of the shoulder girdle.

Whatever the reason for migration of fixation devices, it is important to remember that threaded pins and wires almost never migrate and for that reason that kind should be used where they will serve. If smooth pins or wires must be used, bending the end after it has been inserted will not only prevent migration but will keep the device from puncturing the overlying skin.

Summary

In the case here reported a Kirschner wire that had been used in acetabuloplasty of the left hip in a child when three years of age was roentgenographically observed in the abdominal cavity a year later. It was not causing symptoms. At operation it was found to have migrated through the root of the mesentery and into the liver without incident.

REFERENCES

1. Burman, M., Grossman, S., and Rosenak, S.: The migration of a fracture-transfixing pin from the humerus into the mediastinum, Amer. J. Roentgenol., 76:1061, 1956.

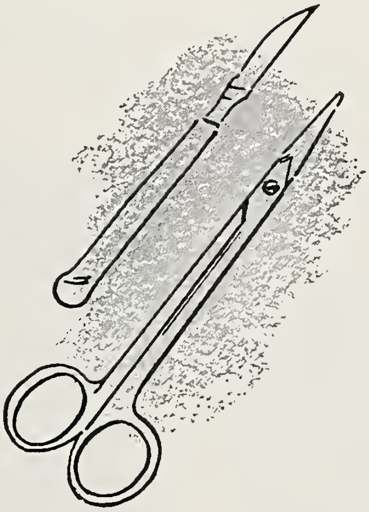
2. Kremens, V., and Glauser, F.: Unusual sequela following pinning of medial clavicular fracture, Amer. J. Roentgenol., 76:1066, 1956.

3. Mazet, R., Jr.: Migration of Kirschner wire from shoulder region into lung: Report of two cases, J. Bone and Joint Surg., 25:477, 1943.

4. McKinnon, W. M. P., Siegman, F. A., and Boley, S. J.: The rectum and vagina as routes of removal of displaced wandering hip nails, Am. Surgeon, 29:905, 1963.

5. Norrell, H., Jr., and Llewellyn, R. C.: Migration of a threaded Steinman pin from an acromioclavicular joint into the spinal canal: A case report, J. Bone and Joint Surg., 47:1024, 1965.

6. Tristan, T. A., and Daughtridge, T. G.: Migration of a metallic pin from the humerus into the lung, New Engl. J. Med., 270:987, 1964.



MEDICAL STAFF CONFERENCE

Malignant Exophthalmos

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. CHARLES M. HASKELL*: The patient is a 33-year-old unmarried x-ray technician with malignant exophthalmos. In August 1964 thyrotoxicosis developed and the patient was given propylthiouracil. Proptosis was noted in November, and subtotal thyroidectomy was done in December. Following this, symptoms of hypoparathyroidism developed and a month later those of hypothyroidism appeared. In March 1965 pronounced malignant exophthalmos developed. Because of the severity of symptoms, prednisone was begun in April and was increased to a maximum of 300 mg a day in May. At that time, steroid diabetes developed. It was controlled with difficulty. The patient then was referred to our thyroid clinic on 10 May. At that time, she had severe exophthalmos (Figure 1).

By June, progressive exophthalmos was apparent and on 28 June the patient entered the hospital with excruciating pain in the left eye, which was dramatically relieved by a local anesthetic agent. Additional history of a paternal grandmother and an aunt with symptoms of thyrotoxicosis was obtained.

At the time of admission, the patient had blood pressure and pulse within normal range. Abnormal physical findings were restricted to the eyes—proptosis, extraocular muscle palsy, severe conjunctival inflammation and decreased visual acuity in the left eye. Visual acuity had decreased from 20/60 early in June 1965 to 20/400 on admission.

Leukocytes numbered 15,600 per cu mm of blood and the serum calcium was slightly decreased. The patient was chemically euthyroid and there was no long-acting thyroid stimulator (LATS) found in peripheral blood.

Two days after admission, left tarsorrhaphy was carried out, and subsequently orbital decompression was done.

DR. LLOYD H. SMITH, JR.*[1]: We are delighted to have Dr. Joseph Kriss as our main discusser of this disorder.

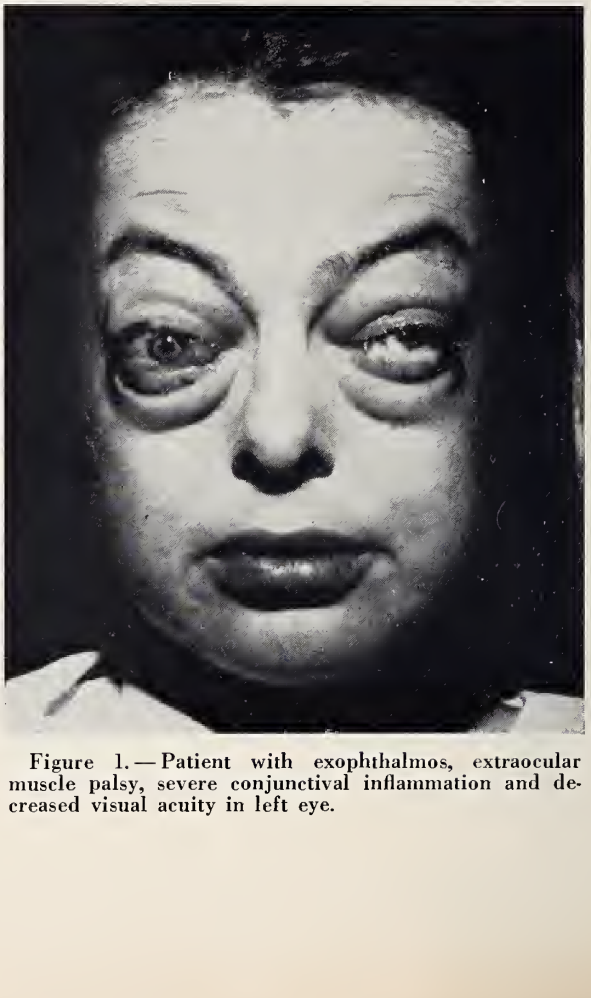


Figure 1.—Patient with exophthalmos, extraocular muscle palsy, severe conjunctival inflammation and decreased visual acuity in left eye.

---

*Intern in the Department of Medicine.

*[1]Professor and Chairman, Department of Medicine.

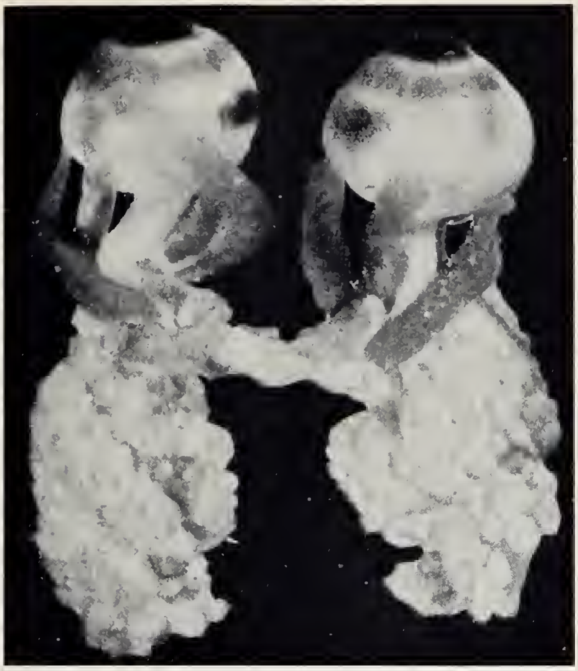


Figure 2.—Dissected orbital contents (including fat, muscles and both globes) from a patient with simple exophthalmos. (From Levitt, T.: The Thyroid, E.N.S. Livingston, Edinburgh, and Williams and Wilkins Company, Baltimore, 1954, page 308. Reprinted with permission of the publisher.)

Dr. Joseph Kriss*[2]: From the history we have just obtained, I believe the patient may have had an episode of thyroiditis before the onset of hyperthyroidism. This might be of some importance in relation to the ophthalmic complications. Pain as a symptom of exophthalmos is not usual. Even in malignant exophthalmos severe pain is distinctly uncommon. These observations raise the question of the development of an ulceration of the cornea associated with local infection. Since corticosteroids can produce an increase in intraocular tension, one might wonder whether glaucoma was present and caused pain. However, corticosteroids usually produce a symptomless increase in tension. Corticosteroids do increase the susceptibility to infection with herpes simplex virus. Since the patient when first observed had very red-looking eyes and leukocytosis, the possibility of a viral infection involving the cornea at the time she had pain should also be considered. It is interesting that a local anesthetic agent dramatically relieved the pain, a fact that would tend to substantiate the idea that pain was due to an ulcer.

Figure 2 shows the dissected orbital contents, including the fat, the muscles and both globes, from a patient with simple exophthalmos often associated with hyperthyroidism and usually not accompanied by the signs and symptoms you have heard described. Figure 3 shows the dissected orbital contents from a patient with an ophthalmopathic condition similar to that observed in the patient whose case we are considering here. Notice in this specimen the extraordinary degree of the swelling of the extraocular muscles. These are edematous muscles: The fact that they are so swollen is probably related to their very high mucopolysaccharide content. This material is hydrophilic. Because there is no place for the orbital contents to go except forward, the increased pressure causes protrusion. Muscle swelling is not really confined to the orbital contents; if one examines skeletal muscle, or even cardiac muscle or skin, one may also find high mucopolysaccharide concentrations. The condition of the tissues resembles rather closely that found in circumscribed pretibial myxedema, which is also associated with a high mucopolysaccharide content and a tendency for edema to form in the legs. These two conditions, exophthalmos and pretibial myxedema, are very commonly associated in the same person. Pretibial myxedema invariably occurs when there has been hyerthyroidism at one time or other, but it does not usually form when the hyperthyroidism is active. It more often appears later. Similarly, the exophthalmos of the type shown today occurs after

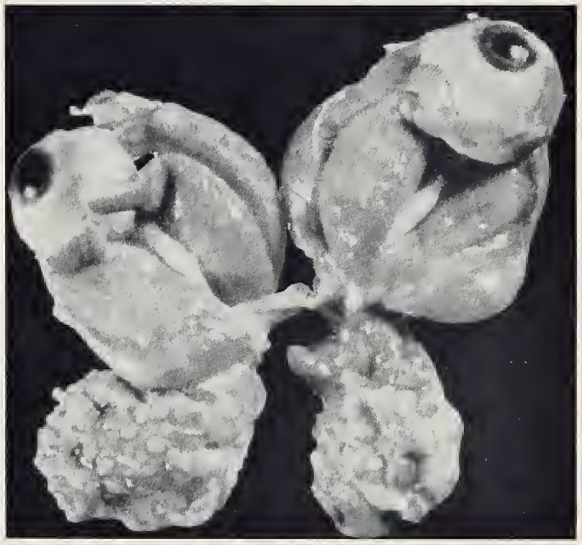


Figure 3.—Dissected orbital contents from a patient with an exophthalmopathy similar to that in case herein presented. (From Levitt, T.: The Thyroid, E.N.S. Livingston, Edinburgh, and Williams and Wilkins Company, Baltimore, 1954, page 308. Reprinted with permission of the publisher.)

---

*[2]Professor of Medicine and Radiology at Stanford University.

treatment for hyperthyroidism more often than before. For these reasons there has been some inclination, and I think probably correctly so, to view exophthalmos as a local manifestation of a general disorder involving connective tissue.

Our interest in this subject has been focused upon the pretibial lesions. Some years ago when testing the serum of a patient for thyroid stimulating hormone (TSH), we found that the serum stimulated the thyroid glands of mice with an abnormally long response. This material has been called long-acting thyroid stimulator. When TSH is injected into a suitably prepared animal and blood radioactivity is subsequently measured, the response is maximal at three hours, lower at 24 hours and absent thereafter. The serum of the previously mentioned patient who was tested several years ago behaved in an anomolous fashion; although it produced a response at three hours, it produced a higher response at 24 hours, which persisted for 48 hours. This prolonged response is characteristic of LATS. Having found this material in one patient with pretibial myxedema, we looked for other persons with this disorder, and now have studied 24 of them. LATS is almost invariably present in patients who have pretibial myxedema. All of the patients with LATS have also had progressive exophthalmos, although not as severe as that observed in the patient we are considering today.

I can summarize a great deal of work done in our laboratory and those of others by describing LATS as a protein of the gamma globulin class. This observation was surprising and raised the question as to whether LATS was an antibody. Until the time of this observation, LATS had been considered a hormone, differing from TSH only in the duration of action. Subsequently, the whole question of the origin of this material and its relationship to both the pretibial myxedema and exophthalmos was open to exploration from a new point of view. Presenting evidence that LATS interacted with thyroid tissue, we offered a hypothesis that the antigen was normally a suppressor of thyroid function. Upon the interaction of the antigen with LATS, thyroid function might be accelerated. Antigen-antibody complexes might be deposited in tissues, such as skin, or in the extraocular muscles, and a reaction of injury of a chronic type associated with deposition of mucopolysaccharide might be initiated. This is highly theoretical, and the antigen is not yet in hand.

Dr. David Solomon and his associates have recently shown that a component of thyroid microsomal fraction appears to bind to LATS. However, the theory still required the demonstration that LATS could be shown to develop in LATS-negative persons. Two years ago, we began a study of patients who had hyperthyroidism. At intervals after radioiodine treatment we observed the serum levels of LATS. Before I^{131} treatment, only one patient had a detectable LATS level. This is characteristic of our experience; we find LATS present in only about 10 to 20 per cent of specimens from thyrotoxic patients. My present view is that LATS does not cause hyperthyroidism but is the result of some thyroid injury. After the radioiodine treatment, LATS appeared in three patients and in one of the three pretibial myxedema developed two weeks after the demonstration of a very high LATS titer. Decided proptosis and other signs of ophthalmopathy developed in the three patients in whom LATS titers appeared. Our findings indicated that LATS could appear in a person who previously did not have it—at least it could appear after radioactive iodine treatment, may be looked upon as a form of thyroid "injury." LATS appeared several months after the treatment. This time course is also characteristic of the natural incidence of exophthalmos and pretibial myxedema.

At about the same time these observations were made, we had an opportunity to study another unusual patient. A child was born to a woman who had undergone a thyroidectomy for thyrotoxicosis in the first trimester of pregnancy. The mother had had thyroiditis preceding the appearance of hyperthyroidism. At birth, the child was thyrotoxic. He appeared wasted and he had congestive heart failure. There was a very small goiter and the periorbital tissues were decidely edematous and inflamed. In the newborn the diagnosis of exophthalmos is difficult because the orbit is only about one-third formed in the newborn infant whereas the globe is about nine-tenths its normal size; for these reasons newborns may appear to have exophthalmos. The baby was treated with antithyroid drugs, oxygen and digitalis. We measured the LATS level in the serum of the baby and the mother. The level in the child's serum fell exponentially with a half time of six days, faster than normal gamma globulin of exogenous origin would fall in a newborn. Perhaps the turnover of LATS was faster than that of gamma globulin because of the hyperthyroidism and because LATS has a specific target—the thyroid. LATS was found in the mother and up to the present time its concentration has not changed from the original level. After the thirtieth day, the child was entirely well, despite withdrawal of therapy. Our conclusion was that LATS is passed transplacentally and that in this instance it induced hyperthyroidism and periorbital edema (and exophthalmos?) in the infant. As the material disappeared from the blood of the child there was a spontaneous cure of both hyperthyroidism and exophthalmos.

In my view the evidence to date supports the hypothesis that LATS is an antibody and there is an intimate relationship between LATS, pretibial lesions and exophthalmos. Systemic corticosteroids will lower the LATS level and occasionally will be effective in inducing a remission in exophthalmos, particularly of the chemosis and the conjunctival injection components. Exophthalmos usually persists for about three to five years and then gradually diminishes. A similar decline occurs in the lesions of pretibial myxedema and in LATS titers. Thus, these three conditions—exophthalmos, pretibial myxedema and LATS serum concentration—are associated in a similar temporal sequence.

Now as to the case that was presented today, one must ask why the LATS titer was negative when exophthalmos was so severe. The LATS measurement was made at a time she was receiving large amounts of corticosteroids. Such treatment will often lower the LATS titer and even result in a disappearance of detectable circulating LATS in many patients. It has also been suggested that the method of LATS assay is not sufficiently sensitive to detect the low levels which may still be responsible for hyperthyroidism or its complications.

DR. LLOYD SMITH, JR.: There is time for a few questions and comments.

Physician in audience: Sir, where do you believe this LATS is produced?

Dr. Kriss: We believe that, like other antibodies, it is produced in lymphocytes. Dr. MacKenzie of Canada has taken the lymphocytes from the peripheral blood of patients with LATS, incubated them with phytohemagglutinin and has found LATS in the incubation medium. We have not succeeded in doing that, however. Furthermore, we removed a lymph node from the perithyroidal region in one patient who had the highest LATS titer we had ever observed, and were unable to demonstrate LATS in the lymph node or in the culture medium.

DR. JAY A. NADEL*[3]: Does LATS injected locally cause the pathological changes you have described?

Dr. Kriss: We have not tried the experiment you suggest in man. Injection of LATS into mice over a period of weeks results in no lesions; but antibodies to the injected gamma globulin are formed, and these may prevent pathological changes from developing.

Editor's Note: Since orbital decompression, the patient has been following a regimen consisting of daily doses of 120 mg of USP desiccated thyroid, 6 gm of calcium gluconate and 10,000 units of vitamin D by mouth and 80 units of NPH insulin intramuscularly. Exophthalmos has not progressed and visual acuity is 20/40 in both eyes. The patient has resumed an active life.

---

*[3]Assistant Professor of Medicine.

California
Medicine

Editor
DWIGHT L. WILBUR, M.D.

Assistant to the Editor
ROBERT F. EDWARDS

For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MacLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

EDITORIAL

The Rubella Nightmare

THAT RUBELLA (German measles) in early pregnancy damages the fetus was first brought to the attention of the medical profession in 1941 by the Australian ophthalmologist Norman Gregg,[2] who showed it to be a prolific cause of blindness, mainly from cataracts, as well as of congenital malformation of the heart. Swan,[6] another Australian, soon amplified the list of fatal injuries by noting deafness, deafmutism, microcephaly with mental deficiency, and physical underdevelopment. The danger period in fetal life was then defined as the first trimester, and it was tacitly assumed that after this time infection of the fetus subsided. The American pandemic of 1964-65 with its estimated 2,500,000 cases and 20,000 damaged infants told a different story and brought into light what is now known as the rubella syndrome.[5] Infection in the fetus (which included the placenta) was found to last not only through the rest of fetal life but, in surviving infants, for many months after birth. About 29 per cent of such infants died at or soon after birth. A hitherto unrecognized symptom complex emerged: thrombocytopenic purpura, jaundice, enlarged liver with hepatitis and enlarged spleen, areas of bone rarefaction, myocarditis, encephalitis and glaucoma were added to the previously well known complications. The continuance of active infections made these infants virus carriers who were a menace to other infants in the nursery, to nurses, to physicians and, indeed to any other persons, including pregnant women, with whom they might come in contact. In general rubella has been shown to have approximately 50 per cent communicability on direct exposure.

It has been shown that more than one pregnant woman in six is susceptible to rubella. One well documented clinical study showed the risk of fetal defects from rubella to have been 47 per cent during the first month of pregnancy, 22 per cent in the second and 7 per cent in the third. Another study[7] based on histological examination in cases of therapeutic abortion performed for rubella during the first four weeks showed that 80 per cent of the products of conception were affected. To the estimates of defects manifest at birth must be added an increment estimated at 50 per cent for defects discovered later, notably deafness which may not be discovered and properly dealt with until the school years. As early as 1962, before the "rubella syndrome" was recognized, Ingalls[3] in discussing maternal rubella in the first trimester stated that "the risks are simply unacceptable."

Through the daily press and such popular periodicals as *Life* and *Reader's Digest* the public has become well informed of the rubella problem and there are few women who have rubella or are even exposed to infection during the early stages of pregnancy who are unaware of the risks involved. Such women face six to nine months of anxiety, often agonizing, unless the pregnancy is terminated spontaneously or therapeutically. The chances that Nature will lend a helping hand by means of spontaneous abortion or stillbirth are, according to recent study, almost negligible.

This brings up the problem of therapeutic abortion. The California statute, which dates from 1872, explicitly states that the only exception to criminal liability for the therapeutic abortion is when "the same is necessary to preserve her [the mother's] life"; but places the burden of proof for nonnecessity on the State. The assumed rigidity of this law and its obstruction to the best medical practice have been long evident, particularly in the cases of incest, rape and various serious, while not immediately life-threatening, disorders of pregnant women; but it was not until the recognition and general awareness of the hazards of rubella (and more recently of thalidomide) to the fetus which we have recounted, that the necessity of modernizing the statute has become urgent. The House of Delegates of the California Medical Association has officially recommended changes to the California Legislature on three occasions, in 1962, 1963 and 1966. The latest of these recommendations, adopted at the March 1966 meeting, reads as follows: Whereas, resolutions were adopted in 1962 and 1963 (30-62, 37-62, 94-63) supporting the concept of medically justifiable abortion in this state; now, therefore, be it

Resolved: That this House reaffirm its position and express to the State Legislature its belief in the broadening of the therapeutic abortion law, taking into consideration the health of both the mother and the product of conception; and be it further

Resolved: That such legislation should provide proper medical control through established hospital staffs or component medical society committees.

On 6 June 1966 the Board of Directors of the San Francisco Medical Society approved the resolution of the House of Delegates of the CMA and added:

"That the Board of Directors of the San Francisco Medical Society believes that it is an acceptable standard of medical practice in this community to perform therapeutic abortions in accredited hospitals in cases of proven rubella, with therapeutic abortion committee approval."

Meanwhile, two obstetricians of high professional and ethical standing, after official sanctions by the appropriate committee of their respective, fully accredited hospitals, performed abortions on patients who had had rubella during early pregnancy, and publicly reported their actions. For this they have been required to appear before the Board of Medical Examiners, which has the power to convict them of unprofessional conduct and revoke their licenses to practice. At the moment of writing, the California State Supreme Court has issued a delay. Apart from the legal aspect of the case, the strictly medical—and humanitarian—indications for abortion seem clear beyond argument, and the need for revision of the law seems impelling. Medical men with an interest in the legal aspects of the problem have read with much interest England's closely related Bourne[1] case in which a physician of the highest professional repute, after consultation with other assenting physicians, performed in a hospital of high standing an abortion on a 14-year-old girl who had been raped in atrocious circumstances, and reported his action to the authorities in the hope of obtaining a modification or reinterpretation of the English law on abortion dated 1861 which allows no exceptions and carries a penalty of penal servitude. After full review the court decided in favor of the physician by liberalizing the interpretation of the law. The court stated that ". . . if the doctor is of opinion, on reasonable grounds and with adequate knowledge, that the probable consequence of the continuance of pregnancy will be to make the woman a physical or mental wreck, the jury are quite entitled to take the view that the doctor, who, in those circumstances, and in that honest belief, operates, is operating for the purpose of preserving the life of the woman." The court made a sharp distinction between such a procedure and criminal abortion.

That ruling in the Bourne case was made in 1938.

In 1955 a conference on abortion was held at the New York Academy of Medicine[4] in which the subject was dealt with at great length and with authority. From this report we quote a statement by Dr. Milton Helpern, Chief Medical Examiner of New York City. (The New York State law on abortion was essentially the same as that in California but put the burden of proof on the defendant.) Dr. Helpern said: "I don't know of a single instance in which an abortion done in an approved hospital, presumably for therapeutic purposes, was ever questioned by the courts. The only cases that I am sure of that are prosecuted are frank criminal abortions."

Finally, we quote a statement by Richard Cardinal Cushing of Boston, cited in a recent issue of the *Reader's Digest:* "Catholics . . . do not need the support of civil law to be faithful to their own religious convictions, and they do not seek to impose by law their moral views on other members of society."

Addendum. As this was being written an Associated Press Dispatch from London in the San

Francisco *Chronicle* dated 23 July 1966 said: "The House of Commons voted overwhelmingly yesterday in favor of a law legalizing abortions where justified by medical advice. . . . The terms of the legislation authorize an abortion where two doctors decide it is necessary for the health of the mother or where there is substantial risk of a child being born deformed. . . . Home Secretary Roy Jenkins . . . told the House there are about 100,000 illegal abortions performed annually in Britain, with the present rigid law unable to cope with the problem."

HAROLD K. FABER, M.D.
The Institute of Medical Sciences
Presbyterian Medical Center
San Francisco

26 July 1966.

Editor's Note: Dr. Faber was for many years professor and head of the Department of Pediatrics at Stanford University School of Medicine. A distinguished pediatrician, he is recognized the world over for his clinical and experimental work in viral diseases.

REFERENCES

1. Calderone, Mary S. (Editor): Abortion in the United States, Paul B. Hoeber, Inc. and Harper and Bros., New York, 1958: The Bourne Case, pp. 193-195.
2. Gregg, N. McA.: Congenital cataract following German measles, Trans. Ophth. Soc., Australia, 3:35, 1941.
3. Ingalls, T. H.: German measles and German measles during pregnancy, Am. J. Dis. Child., 93:555, May 1957.
4. Reader's Digest, May 1966, p. 235.
5. Rubella symposium (20 papers): Am. J. Dis. Childr., 110:345-476, October 1965.
6. Swan, C., Tostevin, A. L., et al.: Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract, deafmutism, heart disease and microcephaly, and to the period of pregnancy in which ocurrence of rubella is followed by congenital abnormalities, Med. J. Australia, 2:201, 1943.
7. Töndury, G., and Smith, D. W.: Fetal rubella pathology, J. Pediat., 68:867, June 1966.

California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 522nd Meeting of the Council, Los Angeles, Airport Marina, 18 June 1966.

The meeting was called to order by Chairman Anderson in the Airport Marina, Los Angeles, on Saturday, 18 June 1966, at 9:15 a.m.

Roll Call

Present were President MacLaggan, President-elect Morrison, Speaker Quinn, Vice-Speaker Telford, Editor Dwight L. Wilbur, Secretary Weyrauch and Councilors Eastman, Todd, Gooel, Taw, Bullock, O'Connor, Rogers, Crum, Boyle, Maguire, Burnett, Richard S. Wilbur, Miller, Watts, Fenlon, Kay, Kaiser, Anderson, Grunigen and Immediate Past President Teall. Absent for cause were Councilors Isenhour, Ham, Yant and Longmire.

A quorum present and acting.

Present by invitation were Messrs. Collins, Thomas, Eberlein, Whelan, Blackley, Clark, Klutch, Hetland, Bowman, Mrs. Redfern and Misses Price and Belser of CMA staff; Mr. Hassard, Legal Counsel; component society executives Scheuber of Alameda-Contra Costa, Rideout of Butte-Glenn, Dalbec of Los Angeles, Collins of Marin, Walters of Riverside, Donmeyer of San Bernardino, Jackson of San Diego, Neick of San Francisco and Marvin of Santa Barbara; Messrs. Saylor, Heller, Babb, Light, Bentley and Potloff of California Physicians' Service; Messrs. Read, Putnam and Brown of the Public Health League; Mr. Gould of the AMA; Doctor Cullen of UC, San Francisco, School of Medicine; Doctor Bauer of USC School of Medicine; Doctor Bostick of UC, California College of Medicine; Doctor Stokes of UC at San Diego, School of Medicine; Mr. Paul Ward, Administrator, State Health and Welfare Agency; Doctor Lester Breslow, Director, State Department of Public Health; Doctor Lowry, Director, State Department of Mental Hygiene; Doctor Skelly, Medical Consultant, State Department of Social Welfare; Doctor Young, Medical Director, State Department of Rehabilitation; Doctor Bushnill, State Department of Rehabilitation; Mr. Henry X. Jackson, President-elect, California Hospital Association; Doctor Gilman, President, Southern California State Dental Association; Doctor Dean, President, California Veterinary Medical

---

JAMES C. MacLAGGAN, M.D. . . . . President
JOHN G. MORRISON, M.D. . . . . President-Elect
WILLIAM F. QUINN, M.D. . . . . Speaker
JOSEPH W. TELFORD, M.D. . . . . Vice-Speaker
CARL E. ANDERSON, M.D. . . . Chairman of the Council
ALBERT G. MILLER, M.D. . . Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D. . . . . Secretary
DWIGHT L. WILBUR, M.D. . . . . Editor
HOWARD HASSARD . . . . Executive Director

General Office, 693 Sutter Street, San Francisco 94102 • 776-9400
ED CLANCY . . . . Southern California Office
1515 N. Vermont Avenue, Los Angeles 90027 • 663-8071

Association; Doctors Burt Davis, Kilroy, Reynolds and others.

1. *Minutes for Approval*

Minutes of the 521st meeting of the Council, held 7 May 1966, were approved with two corrections. These corrections were:

(a) Notation of correct bill number for the "Veterinary Medical Educational Facilities Construction Act," which should be H.R. 490, rather than H.R. 4809.

(b) Notation of the correct referral for House of Delegates resolutions on "Physician-Hospital Relationships" (No. 5-66 etc.). Referral should have read "to Task Force on P.L. 89-97," rather than "to Commission on Communications."

2. *Membership*

(a) On motion duly made and seconded, 5,144 members whose dues were delinquent and now paid, were reinstated.

(b) On motion duly made and seconded, 17 applicants were voted election to Associate Membership. These were: Benjamin Lehr, Imperial County; John Kregzde, Gabriel H. Wilson, Los Angeles County; Robert Moffat Kelsey, Ursula T. Slager, Orange County; Walter J. Bednarz, Oran W. Chenault, Oliver Hayward, David C. Stolinsky, Marie Webster, San Francisco County; Anthony Lapolla, Seward Miller, Santa Barbara County; Clifford N. Felchle, Maurice Rappaport, Santa Clara County; William Cress, Charles B. Fowler, Santa Cruz County; and R. Lynn Knight, Tulare County.

(c) On motion duly made and seconded, five members were voted election to Retired Membership. These were: David Harold Fink, Myron Williams Husband, Monterey County; Rea Chittenden, Orange County; Wilber F. Swett, San Francisco County; and William F. Knorp, San Mateo County.

(d) On motion duly made and seconded, a reduction of dues was voted for 13 members for reasons of prolonged illness or postgraduate education.

3. *Treatment of Workmen in Student Health Centers*

Councilor Joseph Maguire discussed the problem of student health centers providing and charging for treatment of workmen employed by contractors working on various campuses of the University of California. Doctor Maguire explained that this policy directly affects the private practice of medicine although only workmen with minor injuries are being treated in this manner. He suggested that the Committee on Occupational Health and Rehabilitation investigate the situation and report back to the Council so that it might take action on the subject.

ACTION: Voted to refer the problem to the Committee on Occupational Health and Rehabilitation, with instructions to study and report back to the Council.

4. *State Health and Welfare Agency*

Mr. Paul Ward, administrator, State Health and Welfare Agency, presented a progress report on the California Medical Assistance Program (CAL-MAP). During his discussion, Mr. Ward said that there has been a minimum of serious problems since the program was inaugurated 1 March, in spite of the tremendous scope of the program and the rapidity with which it was implemented. He did, however, enumerate four serious problems: Keeping all interested groups informed, implementing the "prepayment" feature of the law in terms of Article 24 of the State Constitution, dealing with liens and attachments for funds filed against the carrier, and obtaining Federal matching funds for the medically indigent who are not categorically linked. Mr. Ward discussed two of these problems in some detail:

(a) *Article 24 of the State Constitution* — Mr. Ward explained that this section states, in effect, that no task can be performed by contract with an outside agency that can be performed by State employees. State employees cannot insure a prepaid health program, but they might be held by the courts to be able to perform the duties of fiscal administrator.

(b) *Federal matching funds* — In providing background for this problem, Mr. Ward pointed out that Congress had provided in Title 19 of Public Law 89-97, matching funds only for those medically indigent who resemble beneficiaries of one of the categorical aid programs. Mr. Ward asked for CMA's support in securing Congressional action, as soon as possible, to include all medically needy persons rather than only those who are "linked" to a category.

ACTION: Voted to appoint a special committee to consider the proposal and report back during the afternoon session of the Council.

Chairman Anderson appointed Doctor Teall as chairman of the committee and Councilors Boyle, Miller, Telford and Todd as members.

5. *Report of the President*

President MacLaggan reported on several meetings he had attended since the last meeting of the Council. Among these was the 18 May meeting of the Commission on Medical Services, at which the proposed CMA Appeals/Review Committee was discussed. Doctor MacLaggan presented the recommended format and makeup of the Appeals/Review Committee for Council approval.

ACTION: Voted to approve the proposed format for the CMA Appeals/Review Committee, with the following members: Homer C. Pheasant, Chairman, Los Angeles; H. Dean Hoskins, Oakland; Wallace A. Gerrie, Jr., Newport Beach; Robert L. Watson, Jr., Los Angeles; Roger C. Isenhour, San Diego; A. J. Murrieta, Jr., Los Angeles; Maurice S. Salomon, San Francisco; Glenn A. Pope, Sacramento; Leo Bell, San Mateo; Joseph F. Boyle, Los Angeles; William H. Thompson, San Mateo; Eli A. Layon, Brawley; Milo A. Youel, San Diego; Richard L. Taw, Los Angeles; Albert G. Clark, San Francisco; George Babbin, Sacramento; Ralph Burnett, Bakersfield; Arthur F. Howard, Fresno; F. M. Brunemeier, Redding; Robert L. Taylor, Oakland; and Leonard R. Ortega, Oakland.

Doctor MacLaggan reported that the Board of Trustees of the California Medical Education and Research Foundation had voted to allocate $2,500 (made available by Audio-Digest) to the library of the Los Angeles County Medical Association to carry out a study on the value of tape recorded information. He further reported that on behalf of CMA, he had sent telegrams to both U.S. Senators from California and to deans of medical schools in California, urging them to join CMA in opposing Senate Bill 2322, pertaining to restrictions on the use of laboratory animals in medical research.

6. *Appointment of New AMA Alternate Delegate*

It was brought to the attention of the Council that the death of Doctor Nicholas V. Oddo of Long Beach created a vacancy among the CMA Alternate Delegates to the AMA.

ACTION: Voted to appoint Doctor Vincent P. Carroll of Laguna Beach to fill the unexpired term of Doctor Oddo.

7. *Committee on Committees*

Chairman Morrison requested Council approval for changing the name of the Committee on School Health to "Committee on School and College Health."

ACTION: Voted to change the name of the Committee on School Health to "Committee on School and College Health."

Doctor Morrison offered the following nominations, most of them to fill vacancies or to supplement membership on various CMA Commissions and Committees:

Liaison Committee to CMAA—Richard Schug of Long Beach, named Chairman

Commission on Allied Health Professions and Services — Richard Schug, Long Beach, viz Charlotte Baer

Committee on Paramedical Personnel—Richard Schug, Long Beach, viz Charlotte Baer

Committee on School Health — Henry Bruyn, Berkeley, viz Deane Adams

Committee on Cardiovascular Diseases — John Connolly, Los Angeles, Consultant

Committee on Auto and Traffic Safety—Robert Tour, San Francisco, viz Constantine Bricca, Jr.

Scientific Board—Arthur Clinco, Los Angeles, viz Stuart C. Knox, and R. Theodore Bergman, viz John Schulte

Committee on Nominations—Robert Prentiss, San Diego, viz Stuart Knox

Statewide "543" Committee on Health Facility Planning—Forest J. Grunigen, Los Angeles, as CMA representative

ACTION: Voted approval of the above nominations and appointments.

8. *Report of the President-Elect*

President-Elect Morrison reported on various meetings he has recently attended, including a meeting of a joint subcommittee of the Task Force on Medical Services and Institutional Facilities (Health Review and Program Council). At this meeting, the joint subcommittee discussed the problem of developing criteria under which "free-standing" clinics could qualify for reimbursement under A.B. 5. They asked that CMA give guidance in resolving the problem.

ACTION: Voted to refer the problem of developing criteria for "free-standing" clinics to the Task Force on P.L. 89-97, with instruction to appropriate, if necessary, resources of other CMA Commissions and Committees.

9. *Health Facilities Planning*

Prompted by President-Elect Morrison's comments on a recent meeting of the National Commission on Community Health Services, there was discussion on recent developments and problems regarding voluntary health facilities planning.

ACTION: Voted to charge the Commission on Hospital Affairs with responsibility for taking action in three areas: (a) Making concrete recommendations to the Council on increasing physician interest and participation in voluntary health facilities planning, (b) giving increased attention to, and reporting back on, the problems created by proprietary hospitals and physician-owned (or controlled) hospitals, (c) studying the ethical ramifications of CMA members practicing medicine in hospitals which provide substandard care.

10. *New Appointments at UC Medical Center, San Francisco*

Councilor Watts introduced Doctor Stuart C. Cullen, newly appointed dean of the San Francisco Medical Center, University of California, replacing Doctor William O. Reinhardt, Doctor Cullen called to the attention of the Council other newly appointed UC officials: Doctor Willard C. Fleming, who succeeds Doctor John B. deC. M. Saunders as Chancellor; Harold A. Harper, Ph.D., Vice Chancellor, Graduate Studies and Research; and Doctor Leslie L. Bennett, Vice Chancellor, Academic Affairs. Doctor Cullen paid tribute to the outstanding contributions of Doctor Reinhardt during, and prior to, his term as dean.

11. *State Department of Public Health*

Doctor Lester Breslow, director, State Department of Public Health, reported that the department hopes to launch a statewide campaign aimed at the eradication of measles. He endorsed a CMA-sponsored research project to document the important role physicians play in discouraging cigarette smoking among their patients.

12. *State Department of Mental Hygiene*

Doctor James Lowry, director, expressed the appreciation of the department for the work being done by CMA in surveying local mental health programs. He also remarked on a study being conducted by the department of the impact of local mental health programs on admissions to State mental facilities. Doctor Lowry pointed out that this year, in spite of population growth, admissions to State mental hospitals have decreased. His final comments were directed toward the limited mental health benefits in A.B. 5 and P.L. 89-97—creating a situation where some patients are being forced out of local, private care into public facilities. There was general discussion of the problem.

ACTION: Voted to refer the problem to the Commttee on Mental Health, asking that it report back with specific recommendations for changes in the laws or regulations.

13. *California Hospital Association*

Mr. Henry X. Jackson, President-Elect of the California Hospital Association, discussed the proposed formation of a voluntary California Health Manpower Council, which would provide a vehicle for voluntary health organizations and State governmental agencies to cooperate in a program designed to increase the supply and quality of health manpower of all kinds.

The proposed organization would be concerned with manpower training and utilization as well as recruitment.

Mr. Jackson briefly discussed several other subjects, among them the acceptance by CHA of a three-year Kellogg Grant. The $60,000 grant will be used to develop programs regarding long-term care in community hospitals.

14. *California Physicians' Service*

Doctor Richard S. Wilbur, chairman of the board, presented a brief report on CPS activities in connection with the California Medical Assistance Program (A.B. 5). He reported that of the 2,800,000 CAL-MAP claims received by CPS before 7 June, 1,700,000 had been paid. He also reported that a new and simpler claims form was being developed. Regarding Medicare (Title 18, Part B), Doctor Wilbur stated that the CPS contract with the Federal government had been signed.

Doctor Wilbur moved that the problem of professional coverage for members of CMA be referred to the Commission on Professional Welfare for evaluation. After working with CPS, the Commission would report back to the Council with recommendations.

ACTION: Voted to refer the CPS plan for professional coverage to the Commission on Professional Welfare, with instructions to consult with CPS and report back with recommendations.

15. *Affiliated Organizations and Invited Guests*

Representatives of other affiliated organizations, departments of State government and medical schools reported on activities of interest to the Council and the medical profession. No action was required. Among those present were Doctor Stuart Cullen, new dean of UC, San Francisco Medical Center; Doctor Warren Bostick, dean of the UC-California College of Medicine; Doctor Franz Bauer, associate dean, USC School of Medicine; Doctor John Skelly, medical consultant, State Department of Social Welfare; Doctor Richard Young, medical director, State Department of Rehabilitation; Doctor Bushnill, State Department of Rehabilitation; Doctor C. W. Gilman, president, Southern California State Dental Association; and Doctor Ben Dean, president, California Veterinary Medical Association.

16. *Report of the California Delegation to AMA*

Doctor Burt L. Davis, chairman of the California delegation to the American Medical Association, reported that because of its increasing size, the delegation was becoming more formal in its organization. He remarked on the advantages of joint meetings between the delegation and the CMA Council and announced that, in spite of efforts to condense subjects for resolutions as much as possible, the Delegation would be going to the AMA Convention with 21 resolutions.

17. *Medical Executives Conference*

Mr. Reuben Dalbec, conference chairman, presented the name of Mr. Donald Sower, for consideration for membership in the conference. He announced that Mr. Sower will replace Edward Collins as executive secretary of Marin Medical Society. Mr. Collins will be joining the CMA staff.

ACTION: Voted Mr. Donald Sower a member of the Medical Executives Conference.

18. *Federal Matching Funds for CAL-MAP Beneficiaries*

Doctor Ralph Teall, who had been appointed chairman of a special committee to consider a request by Mr. Paul Ward, administrator, State Health and Welfare Agency, reported recommendations of the committee. Regarding the CMA's support in securing action by Congress on its implied commitment to include grants for medical care of all medically needy persons instead of only those "linked" to a category, the committee recommended that:

(a) No resolution be submitted by the Council to the CMA Delegation to the AMA on the subject of Federal matching funds for additional population under P.L. 89-97, Title 19.

(b) The CMA Delegation be requested to take whatever action seems most appropriate at the AMA meeting 26 to 30 June to support Congressional approval for the necessary matching funds for medical care of all medically needy persons, and

(c) CMA officers and other CMA representatives to AMA or advisors to governmental agencies exert their influence to accomplish this end.

ACTION: Voted approval of the above recommendations.

19. *Bureau of Research and Planning*

In the absence of Chairman Sherman, the report of the Bureau was given by Mr. Murray Klutch. It was recommended by the Bureau that the Council authorize the distribution of a 22-page *Summary* of Doctor Magraw's book, *Ferment in Medicine,* to members of the Committees on the Role of Medicine in Society and Organizational Review and Planning, as well as to presidents, secretaries and executives of county and district medical societies in California.

ACTION: Voted to authorize the distribution of the* Summary *to the above named committees and individuals.

Mr. Klutch also reported that the Bureau of Research and Planning had been asked by the State Department of Public Health to conduct a study among a representative sample of physicians in California on techniques employed by practicing physicians to discourage their patients from smoking. The Bureau would be responsible for developing a questionnaire, conducting the study and analyzing the results; the study would be financed by the State Bureau of Chronic Diseases. Mr. Klutch pointed out that this request is in accord with House of Delegates Resolution 73-66 (smoking and health educational activities). Because the resolution had previously been assigned to the Commission on Community Health Services, it was suggested that the Bureau seek the advice of the Commission in developing the questionnaire.

ACTION: Voted to authorize the Bureau of Research and Planning to proceed with negotiations for development of the study, working in cooperation with the Commission on Community Health Services.

20. *Task Force on P.L. 89-97*

Chairman Teall reported that regulations for CAL-MAP (A.B. 5) are still undergoing modification and some problems are not resolved. He pointed out that the regulations published 1 March 1966, are available in quantity from the State Printing Office.

21. *County/Teaching Hospitals—Staff Relationships*

After some discussion, Councilor Boyle moved that the Council endorse the concept that the CMA cooperate with Los Angeles County Medical Association in conducting a study of the legal and ethical considerations involved in contracts between physicians and partnerships in a teaching hospital or clinic situation.

ACTION: Voted to approve the cooperative effort.

22. *Committee to Study the Role of Medicine in Society*

On behalf of the Committee to Study the Role of Medicine in Society, Chairman Watts reported that, since previous studies of the Committee have been analytical in nature, the present year could be devoted to actions that might be taken.

Doctor Watts also said that with respect to Resolution 57-66 and 64-66 (accreditation of voluntary health insurance plans), previously referred to the Committee to Study the Role of Medicine in Society, the Committee endorses the intent of both resolutions and recommends that the Council urge implementation of this intent through the California Delegation to the AMA.

ACTION: Voted to accept the recommendation of the Committee.

Chairman Watts also reported that the Committee had voted to recommend that the Council consider, as one topic for the special September meeting of the Council, a discussion with the chairmen of the various commissions and committees of the manner in which decisions are reached within the CMA.

23. *Commission on Medical Services*

In the absence of Chairman Howard, the report of the Commission was presented by Councilor Burnett. It was reported that there had been much discussion by the Committee with General Peatfield of the Office of Dependents' Medical Care (ODMC) regarding the concept of "usual and customary" fees, ODMC refused to contract on that basis at this time, but did agree to a new contract for the fiscal year 1966-67 based on a coefficient of $5.50 in relation to the 1964 *Relative Value Studies.*

The Committee recommended and the Commission concurred that CPS be directed to accept this proposal and that the Office of Dependents' Medical Care be notified that the CMA is on record as desiring full implementation of the "usual and customary" fee concept.

ACTION: Voted to accept the recommendation of the Commission.

24. *Commission on Community Health Services*

Chairman Kay presented the report of the Commission and referred the Council to the attachment included in the report of the last Commission meeting, which was a reprint of part of the Bryan Report dealing with the formation of a Community Health Council. A discussion followed on the topics of a Community Health Council and a Health Manpower Committee.

Although the Council had, at its last meeting, approved in principle the formation of a Community Health Council, Chairman Kay felt that this should receive further discussion and consideration due to the magnitude of such an effort and the funds that would be involved. It was decided that further study should be given to the formation of a State Health Council, and that the Commission on Community Health Services should carry this out and report back to the Council at the next meeting with more concrete suggestions. It was moved that the Chairman of the Council refer the CHA proposal for a Health Manpower organization to an appropriate committee and report to the Council at the next meeting.

ACTION: Voted that the Council Chairman assign the Health Manpower organization to the appropriate committee, with instruction to explore the proposal and report back at the next meeting of the Council.

25. *Commission on Allied Health Professions and Services*

Councilor Melone, Chairman of the Committee on Paramedical Personnel, gave a report on two recommendations made by that committee. The first recommendation was to modify the CAL-MAP regulations to include under the program registered physical therapists in private practice. It was moved that the amended statement prepared by the Committee on Paramedical Professions be accepted with the insertion of the word "registered" preceding the words "physical therapist."

ACTION: Voted to accept the statement as amended.

The Committee also recommended and the Commission concurred, that Resolution 61-66 be implemented through a letter to the Board of Licensed Vocational Nurse Examiners by the President of the CMA, suggesting that physician participation should be encouraged in LVN training, especially in the area of explaining medical ethics, and offering the CMA's cooperation in this regard.

ACTION: Voted to implement the Resolution as stated.

26. *Commission on Communications*

Chairman Todd informed the Council that the next meeting of the Commission will be on 20 July. He called attention to the forthcoming July issue of CMA News—an 8-page issue devoted to Medicare.

A resolution on therapeutic abortion was introduced by Chairman Todd. The resolution reads:

"Be it resolved, that the CMA Council strongly endorses the resolution passed by its House of Delegates in March 1966, which states that: 'This House reaffirm its position and express to the State legislature its belief in the broadening of the therapeutic abortion law, taking into consideration the health of both the mother and the product of conception. Such legislation should provide proper medical control through established hospital staffs or component medical society committees,'

"And be it further resolved, that the CMA propose legislation for introduction into the 1967 legislature to achieve these objectives."

ACTION: Voted to approve resolution on therapeutic abortion.

27. *American Medical Political Action Committee*

Chairman Todd reported that all 50 states had been represented at the National Workshop of AMPAC held last month in Washington, D. C., and the California delegation was one of the largest. He also announced a CALPAC workshop to be held in Los Angeles on Saturday, 10 September 1966.

28. *Committee on Legislation*

Chairman Kilroy reviewed the efforts of the Committee in preparing for the fall elections. He also reported on the Collier Bill, which deals with implied consent for blood tests of suspected drunken drivers. The Committee on Legislation and the Public Health League have supported this bill, Doctor Kilroy said, as they have supported similar bills that have been introduced in the past.

29. *Staff Report*

Mr. Howard Hassard reported that the audit conducted by the Internal Revenue Service on the records of the California Medical Association for the years 1963-64 had been completed and everything was found to be in order. The auditor recommended that the report be approved.

30. *Utilization Curbs in CAL-MAP*

Council Vice-Chairman Miller commented on a letter from the Sacramento County Medical Society, which called to the attention of the Council that, under CAL-MAP regulations, there is no curbing device to prevent patient overutilization of services. The letter pointed out that Medicare does have such a deterrent in the co-insurance and deductible features, and suggested that a similar type of deterrent should be written into the CAL-MAP regulations. The letter asked that the Council explore this matter.

ACTION: Voted to refer the matter to the Task Force on P.L. 89-97.

31. *Special September Council Meeting*

ACTION: Voted to hold the special two-day meeting of the Council, 17 to 18 September, at the Hotel Del Coronado near San Diego.

32. *Adjournment*

There being no further business to come before it, the meeting was adjourned at 4:35 p.m., in memory of Nicholas V. Oddo, M.D.

Helen B. Weyrauch, M.D., *Secretary*
Carl E. Anderson, M.D., *Chairman*

In Memoriam

ASHCRAFT, GRANVILLE P., Yreka. Died 19 July 1966, in Yreka, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Doctor Ashcraft was a member of the Siskiyou County Medical Society.

✣

CHAMBERS, ELEANOR KATHLEEN, Berkeley. Died 4 July 1966, aged 72. Graduate of Loyola University School of Medicine, Chicago, Illinois, 1933. Licensed in California in 1933. Doctor Chambers was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

GARFIELD, F. EDWYN, San Francisco. Died 25 July 1966, aged 64. Graduate of Northwestern University Medical School, Chicago, Illinois, 1928. Licensed in California in 1928. Doctor Garfield was a member of the San Francisco Medical Society.

✣

GEHRES, ROBERT F., Sacramento. Died 30 July 1966, in Sacramento, aged 51. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1941. Licensed in California in 1947. Doctor Gehres was a member of the Sacramento County Medical Society.

✣

HINMAN, HARRY THORNTON, JR., Shasta. Died 27 July 1966, in an airplane crash, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1939. Doctor Hinman was a member of the Shasta-Trinity County Medical Society.

✣

ISNARDI, MARIO, San Francisco. Died 28 July 1966, in San Francisco, aged 85. Graduate of Facolta di Medicina e Chirurgia dell'Universita di Torino, Torino, Italy, 1905. Licensed in California in 1906. Doctor Isnardi was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

KAPLAN, MAX, Los Angeles. Died 25 July 1966, in Los Angeles, aged 69, of coronary artery disease and uremia. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1919. Licensed in California in 1919. Doctor Kaplan was a member of the Los Angeles County Medical Association.

✣

LOPIZICH, IVO JOHN, Los Angeles. Died 22 July 1966, in Los Angeles, aged 72, of heart disease. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1920. Licensed in California in 1922. Doctor Lopizich was a member of the Los Angeles County Medical Association.

✣

MCCLURKIN, ARTHUR ARCHIBALD, Los Angeles. Died 17 July 1966, in Los Angeles, aged 76, of congestive heart failure. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California School of Medicine, Los Angeles, 1917. Licensed in California in 1917. Doctor McClurkin was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

MCLAUGHLIN, TILMAN HENRY, Los Angeles. Died 23 July 1966, in Los Angeles, aged 90, of arteriosclerotic cardiovascular disease. Graduate of Illinois Medical College, Chicago, 1903. Licensed in California in 1920. Doctor McLaughlin was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

✣

ROBARTS, HARRY P., San Francisco. Died 23 July 1966, in San Francisco, aged 88. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1903. Licensed in California in 1903. Doctor Robarts was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

RUBENSTEIN, HARRY, Canoga Park. Died 24 July 1966, in Canoga Park, aged 50, of heart disease. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1950. Licensed in California in 1950. M.D. degree from California College of Medicine, 1962. Doctor Rubenstein was a member of the Los Angeles County Medical Association.

✣

SMITH, W. BURR, Los Angeles. Died 4 June 1966, in Los Angeles, aged 73, of hepatitis. Graduate of the College of Physicians and Surgeons, San Francisco, 1920. Licensed in California in 1921. Doctor Smith was a member of the Los Angeles County Medical Association.

✣

WHITTAKER, LAWRENCE F., Huntington Beach. Died 24 July 1966, in Huntington Beach, aged 64, of coronary artery disease. Graduate of the University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1929. Doctor Whittaker was a member of the Orange County Medical Association.

Television—The Newest Medium for Continuing Education in Medicine

DONALD BRAYTON, M.D., *Los Angeles*

A NEW ERA in continuing medical education opened 26 October 1965 in Southern California. At 8 o'clock that morning the first medical program was broadcast using the closed circuit ("scrambled image") facilities of The Medical Television Network. This first broadcast, like others to follow, occupied one hour, the latter part of which was devoted to telephoned questions from viewers, broadcast and answered "live" by the program participants.

The use of electronic audio-visual equipment in education has been expanding since World War II. Medical schools have availed themselves of such devices increasingly during the past 15 years, usually by interconnections within the campus or between the school and an affiliated hospital using wired microwave systems. Actual broadcast of material for continuing education in medicine has appeared more recently in widely separated areas of the United States. These programs are usually associated with medical schools. All such projects use the facilities of one or more local educational television stations for open broadcast, usually during the late evening, to eliminate public viewing as much as possible. Such medical broadcasting projects are currently to be found in Boston, New York City, Buffalo, Pittsburgh, Charleston, S.C., and Salt Lake City.

When educational television station KCET, Channel 28, ultra-high frequency (UHF), commenced its operation in Los Angeles in 1964, considerable thought was given to the possible use of its powerful transmitter, strategically located on Mt. Wilson, as a means of projecting educational material in postgraduate medicine. The U.C. Extension Office of Continuing Education in Medicine at Los Angeles especially had been interested for some years in the use of television as a medium for broadening the range of its educational efforts. Since the idea of public broadcast had many obvious disadvantages, it was decided that televised medical subjects should be protected from public view by using a "scrambled image" broadcast, and decoding or "unscrambling" both the video and audio at the points of reception. Following a pilot project, conducted during the spring of 1965, this method was found to be feasible.

The Medical Television Network was then organized with UCLA Office of Continuing Education in Medicine (U.C. Extension) as the administrative and fiscally responsible member of a group of medical institutions associated for the purpose of production of programs. The other members of this group of medical television producers are UCLA School of Medicine, U.S.C. School of Medicine, Loma Linda University School of Medicine, City of Hope Medical Center, and U.C. California College of Medicine. Official representatives of these institutional producer members formed the Production Coordination Committee of The Medical Television Network which met first in September 1965 and has continued to meet regularly, functioning as the programming and policy-making body for the network. This committee also has members representing the American Academy of General Practice, the American Cancer Society, the Los Angeles Heart Association, the AMA Advisory Committee on Motion Pictures, Radio and Television, the Tuberculosis and Health Association, and Station KCET.

All major hospitals within range of KCET in the seven Southern California counties of Santa Barbara, Ventura, Los Angeles, Orange, San Bernardino, Riverside and San Diego were invited to join The Medical Television Network as participating hospitals for the reception of broadcasts. Each hospital joining the network selected a coordinator responsible for medical television

---

The author is Assistant Dean, UCLA School of Medicine. and Head of the Office of Continuing Education in Medicine and the Health Sciences, University of California Extension, Los Angeles.

within his institution. These participating hospital representatives meet once yearly or oftener with the Production Coordination Committee to plan ways for increasing the academic excellence and clinical applicability of the material broadcast.

The major portion of the fee assessed each hospital for joining the network was spent for the purchase and installation of the necessary decoding ("unscrambling") and monitoring equipment in each institution. The remainder was used to bolster the financial position of The Medical Television Network, particularly as regards production costs. All teaching hospitals with *bona fide* medical school affiliations were admitted to the network for the cost of the equipment and installation only. Fortunately, additional funding was obtained from the American Cancer Society, the National Institutes of Mental Health, the City of Hope Medical Center, the Tuberculosis and Health Association, and the Los Angeles Foundation of Otology. Receipt of these funds, plus keeping production costs at a minimum, allowed the Medical Television Network to produce and broadcast 30 programs during the 1965-66 academic year at a "break-even" level.

During this period of broadcasting the number of participating hospitals increased to a total of 71. Full credit was allowed by the Academy of General Practice to its members for viewing the programs. Initial technical difficulties with both audio and video were gradually remedied so that by 31 May 1966, the date of the final broadcast of the series, only one hospital, located in San Diego County at the extreme range of the KCET signal, continued to have significant difficulties.

All participating hospitals were asked for reports on attendance, and a majority responded well. The findings of a questionnaire, sent to a random sample of physicians viewing the broadcast, are currently under analysis and will be completely reported at a later date. In general, this study appears to indicate that continuing medical education by scrambled broadcast television is reaching a slightly greater proportion of the total potential range of physicians than is reached by standard educational methods. It also appears that arrangements for viewing at other than the broadcast time (now set weekly on Tuesdays from 8 to 9 a.m.) may significantly increase the viewership. This can be accomplished by the use of a small videotape recorder in each hospital for program playback *ad libitum*. Continued improvement in the quality of the medical programs taped for broadcast is also indicated. For this purpose The Medical Television Network has secured the full-time services of an experienced and talented producer of medical films and television tapes who will work closely with the faculty members of all producing institutions to insure increasing professional excellence in production.

The major requirement to augment medical television viewership is to motivate the physician to attend the programs. Eventually each television program will not only be handily available at the physician's own hospital during the original broadcast but also continuously available thereafter for playback. Production is being carried out with increasing skill to enhance interest.

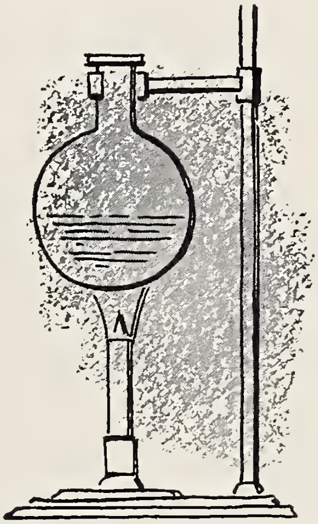
Is it possible to stimulate a physician to view programs that concern fields of medicine other than his specialty? If it were somehow possible to popularize what undoubtedly is a truism, that keeping abreast of medical knowledge in all fields in this easy fashion can have a salutary effect upon a physician's capability to practice his own specialty, the total viewership of medical television might increase rapidly indeed.

The Medical Television Network approaches the 1966-67 "season" with plans in hand and operations under way to produce and broadcast 38 programs weekly, commencing 20 September 1966. The Network has been fortunate in securing a two-year contract with the U.S. Public Health Service which will underwrite a portion of the costs of its operations in return for meticulous statistical reporting. This, plus funding from some other sources previously mentioned, and from the California Dairy Council, will allow the network to reduce its tuition charges to previously participating hospitals by 25 per cent this year.

The advent of the reasonably priced videotape recorder on the commercial market offers The Medical Television Network an excellent opportunity for extension of its medical educational programs both in time and in space. The "time extension" has been referred to previously. This is accomplished by placing a videotape recorder in a hospital within the KCET broadcast range. By taping each broadcast for later playback, the fixed time of the broadcast ceases to be a limiting factor for viewership by many physicians.

The "space extension" using videotape recorders requires that the broadcast "master" videotape be reduplicated on many small tapes suitable for use on the smaller recorders. (The Medical Television Network is currently duplicating tapes for two videotape recorders, each manufactured by a separate concern.) These small duplicated videotapes are then mailed to any hospital anywhere for playback at any time, provided the hospital possesses a videotape recorder. The network has been fortunate in obtaining the requisite tape, as well as reduplication and distribution facilities, at minimal cost. This will allow member (tuition paying) hospitals within the broadcast range to receive a new small videotape each week as a bonus, at no extra cost, provided they have a videotape recorder. Hospitals beyond the broadcast range will be offered 38 videotapes for playback on their recorders at the same tuition required of hospitals within the broadcast range. In this way a hospital hundreds or even thousands of miles from Los Angeles may still benefit from the programs in continuing education broadcast originally in Los Angeles by The Medical Television Network. Each week, for 38 weeks, beginning on or about 20 September 1966, each such hospital will receive a new medical videotape, to be returned to the distributor at the end of the week, when the next tape arrives.

The future of continuing medical education by television appears to be bright indeed. Although precisely the same physician motivation problems are present with television as with all other forms of continuing education in medicine, it seems possible that, with the ubiquity of the television receiver, the increasing availability of good videotape recorders (probably at progressively lower prices), the ease of viewing a broadcast or videotape at one's own hospital, and the gradual improvement in the sophistication of medical television production, the proportion of physicians interesting themselves in this form of education may well increase beyond that now reached by other forms of continuing medical education.



Plan to Attend

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS PLUS THREE GENERAL MEETINGS ON THE SUBJECT:

ADVANCES IN DIAGNOSTIC TECHNIQUE

Capability • Reliability • Integration

THIRD CALL FOR
Scientific Papers
Medical Motion Pictures
Scientific Exhibits

★ **If you have a paper** you'd like to present to your colleagues during their section meeting . . . write today to your section secretary (names and addresses of scientific section officers may be found on page 6, Advertising Section of *California Medicine*). Presentations are not limited to Advances in Diagnostic Technique.

★ **If you have a motion picture or exhibit** . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

PLANS FOR THE 1967 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

PUBLIC HEALTH REPORT

LESTER R. BRESLOW, M.D.
Director of Public Health

THE ANNUAL REPORT on Occupational Disease in California underlines an interesting fact—that more than three-fifths of the 499 occupational disease fatalities in the State's labor force of some eight million persons were due to cardiovascular conditions. This emphasises the need for preventive programs in occupations which aggravate chronic illnesses.

Other causes of death were pneumoconiosis, toxic exposures, coccidiomycosis, tetanus, malignant neoplasms and emphysema.

These facts were drawn from the 27,255 physicians' reports of occupational disease reviewed in 1964. Two new categories, chemical burns and eye conditions attributed to toxic materials, were added to the Bureau of Occupational Health list.

To compare 1964 data with that of previous years, the 8,204 reports of cases in these new categories must be subtracted from the total. The remaining 19,051 physicians' reports represent a 6 per cent increase over the 18,060 reviewed the previous year.

Among the major industrial divisions, agriculture had the highest rate of occupational disease with 12.7 reports per 1,000 workers, followed by construction with 8.4, and manufacturing with 7.7. Within the manufacturing division, rates were prepared for production workers as well as for all workers in a given industry. The risk of occupational disease in manufacturing appears to be greater for production workers than that for all workers.

Skin conditions accounted for over 50 per cent of the 27,255 occupational disease reports received in 1964, eye conditions attributed to toxic materials for over 20 per cent, chemical burns for 10 per cent, respiratory conditions for nearly 5 per cent, and systemic poisoning about 3 per cent.

Diseases in the two new categories, chemical burns and eye conditions due to toxic materials, accounted for almost one-third of the reports reviewed. An analysis of the 3,263 physicians' reports of these conditions received in the first half of 1964 indicated that a sizable reduction in these cases could result if preventive programs were directed toward those places of work using acids, caustics and alcohol solvents.

* * *

More than $233 million in state and federal funds has been allocated for the construction of hospital and health facilities in California since the enactment of the Hill-Burton Hospital Survey and Construction Act 20 years ago. These funds have provided two-thirds financial assistance for the construction of 354 facilities containing 18,684 beds.

The funds have been used for general, tuberculosis and psychiatric hospitals, public health centers, rehabilitation facilities, diagnostic and treatment centers and long-term care facilities. Funds were allocated for the first time last year for community centers for the mentally ill and community facilities for the mentally retarded.

Each year the State Legislature has appropriated funds to match federal construction dollars. In 1946, $3,912,320 in state and federal matching funds was made available. During the current fiscal year, approximately $20 million in matching funds will be available.

The Hill-Burton legislation was enacted in 1946 to meet a critical hospital shortage following World War II. In recent years, program emphasis has shifted to meet the need for modernization and replacing health facilities in densely populated areas, and the construction of additional facilities and beds in rural and economically subnormal areas, Metropolitan and regional planning for facilities is also encouraged.

NEWS & NOTES

NATIONAL • STATE • COUNTY

Thomas C. Paton has been named as the new president of California Physicians' Service-Blue Shield, it was announced by Richard Wilbur, M.D., chairman of the board of CPS.

R. S. "Rusty" Saylor, who retired as head of the Indiana Blue Shield plan last year and has been serving as acting president of CPS since March, will remain at CPS for a time to aid Paton in taking over his new post.

Mr. Paton comes to the California organization from Minnesota Blue Shield, where he has served as chief executive for the past five years. He has been associated with Blue Shield and Blue Cross for about 20 years.

Selection of Paton to head the million-member California Blue Shield plan was made after several months of search and screening for a chief executive. A recognized authority on prepaid medical care, Mr. Paton has held many posts of national significance. He currently serves on the board of directors and the executive committee of the National Association of Blue Shield Plans. He also is on the board and executive committee of Medical Indemnity of America, a subsidiary of the National Blue Shield organization.

Paton was selected for the Medicare Carrier Advisory Committee to the Social Security Administration, and serves on the Joint Contract Administration Board for the Federal Government Employees' Insurance Benefits provided by Blue Shield and Blue Cross.

LOS ANGELES

A $1,575 **tuition scholarship** for one year at Stanford University School of Medicine, given by the **Los Angeles County Medical Association,** has been awarded to Stephen M. Baird of Glendale. The award was announced by Dr. Joseph P. O'Connor, president of the board of directors of the medical association.

A 1966 graduate of Stanford University, Baird was on the dean's list for his sophomore, junior and senior years.

* * *

Dr. Daniel G. Morton of Los Angeles was elected president-elect of the American Gynecological Society at the annual meeting in Chicago. Dr. Andrew A. Marchetti of Washington, D.C., was installed as president.

* * *

The appointment of **Dr. John P. Meehan** as chairman of the Department of Physiology at the University of Southern California School of Medicine was announced last month by Dr. Norman Topping, USC president, and Dr. Roger O. Egeberg, dean of the School of Medicine. Dr. Meehan had been a professor of physiology at USC since 1964.

* * *

The Southern California Psychiatric Society will hold its annual convention at the Hotel Del Coronado in San Diego, November 4, 5, and 6, 1966. Information relating to the meting may be obtained from Dr. Ralph M. Obler, 11860 Wilshire Boulevard, Los Angeles 90025,

SACRAMENTO

A symposium on **tumors in infancy and childhood** will be held September 20 in Sacramento, sponsored by the Sacramento County Medical Society and the American Cancer Society, Sacramento branch. After registration at noon, the program will begin at 1:15 p.m.

Solid Abdominal Tumors—Harold W. Dargeon, M.D., chairman emeritus, Department of Pediatrics, Memorial Hospital for Cancer and Allied Diseases, and clinical professor of pediatrics, emeritus, Cornell University.

The Leukemias—Emil J. Freireich, M.D., professor of medicine and chief, Research Hematology, University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston.

Bone Tumors—Louis Lichtenstein, M.D., clinical professor of pathology, University of California School of Medicine, San Francisco, and professor extraordinario, National University of Mexico.

Central Nervous System Tumors—Byron C. Pevehouse, M.D., assistant professor of neurosurgery, University of California School of Medicine, San Francisco.

At 8:30, during the regular meeting of the Sacramento County Medical Society, B. J. Kennedy, M.D., will speak on **Cancer Research and its Clinical Application.** Dr. Kennedy is associate professor of medicine and chairman of the Cancer Coordinating Committee, University of Minnesota School of Medicine. Further information may be obtained from American Cancer Society, 916-11th Street, Sacramento.

SAN FRANCISCO

Mount Zion Hospital and Medical Center has opened a new 18-bed "open" unit for the **evaluation and treatment of voluntary psychiatric in-patients** and a limited number of day-care patients. The unit will offer a broad range of psychiatric treatment including individual and group psychotherapy, medication, electroshock, an activities program, and family counselling. The charges for care on the unit will be $55 a day for in-patients and $20 a day for day-care.

Further information may be obtained from Mrs. Virginia Price, psychiatric social worker, 567-6600.

GENERAL

The Fourteenth Annual Meeting of the **Pacific Coast Fertility Society** will be held at El Mirador Hotel, Palm Springs, October 13-16, 1966.

Information may be obtained by writing to the office of the Society at 5410 Wilshire Boulevard, Los Angeles.

* * *

Two and a half days of **lectures and workshops in medical and basic science writing** will be held November 11-13, 1966, at Asilomar, Pacific Grove, California, under the sponsorship of the Northern California chapter of the American Medical Writers' Association. The second in a proposed series of intensive courses with limited enrollment, the meeting will feature three speakers who are expert in this specialized field of communication, and each lecture will be followed by small-group clinical discussions of published or unpublished papers offered for criticism by enrollees. Membership in AMWA is not a requirement for enrollment.

Fee for registration, including tuition, meals and deluxe rooms at Asilomar for two nights, is $63 each for two persons in a room, $61 each for three in a room.

For registration or further information, contact: Harley Messinger, M.D., Ph.D., 3029 Benvenue Avenue, Berkeley, California 94705. Telephone 841-8693.

The Physician's BOOKSHELF

BASIC GASTRO-ENTEROLOGY—Including Diseases of the Liver—J. M. Naish, M.D., F.R.C.P., Consultant Physician, Frenchay Hospital, Bristol; Lecturer in Medicine, University of Bristol; and A. E. A. Read, M.D., F.R.C.P., Reader in Medicine, University of Bristol; Honorary Assistant Physician, Bristol Royal Infirmary, United Bristol Hospitals, and South-Western Regional Hospital Board. With chapters by T. J. Butler, M.D., F.R.C.S. and K. T. Evans, M.R.C.P., F.F.R. Distributed in the United States by the Williams & Wilkins Company, Baltimore 2, Maryland, 1965. 351 pages, $11.00.

The authors wrote this book to provide the basic principles and facts of gastroenterology for young doctors interested in learning the elements of gastroenterology. In order not to confuse the reader by presenting both sides of controversial subjects, the authors attempted to give what they consider the middle view, without appearing to be dogmatic. This is a difficult task to encompass in a volume of some 300 pages, and it is therefore to the credit of the authors that they have done an admirable job. The book will prove useful to the physician, surgeon, radiologist, pathologist or physiologist seeking an introduction to clinical gastroenterology.

WILLIAM H. BACHRACH, M.D.

* * *

DISORDERS OF CARBOHYDRATE METABOLISM IN INFANCY—Marvin Cornblath, M.D., Professor of Pediatrics, The University of Illinois College of Medicine, Chicago; and Robert Schwartz, M.D., Associate Professor of Pediatrics, Western Reserve University School of Medicine; Cleveland Metropolitan General Hospital. Volume III in the Series: Major Problems in Clinical Pediatrics—Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, Philadelphia and London, 1966. 297 pages, $8.50.

This is the third book in a series being edited by Dr. Alexander J. Schaffer. The first two books, also reviewed in this journal, were Avery's "The Lung and Its Disorders in the Newborn Infant" and Markowitz and Kuttner's "Rheumatic Fever, Diagnosis, Management and Prevention." This third volume continues the standard of excellence established by the previous two. The field of carbohydrate metabolism in infancy is a relatively new one. A great deal has been learned in the last 10 years, and both Dr. Cornblath and Dr. Schwartz are leaders in this field. This book is particularly timely with the increased interest in hypoglycemia in the neonate.

The book is arranged in five parts. The first part deals with metabolism of carbohydrates in general in a rather abbreviated fashion, goes on to metabolic adjustments in pregnancy, dealing with the mother, the placenta and the fetus, and finally describes carbohydrate homeostasis in the neonate. This method of dealing with the subject in a developmental fashion sets the stage for a discussion of the problems in homeostasis which follow. Part II deals with the clinical problems of adjustments in the neonate, including infant of a diabetic mother, transient symptomatic hypoglycemia in the neonate and a relatively rare entity, transient diabetes mellitus in early infancy. The chapter on symptomatic hypoglycemia in the neonate is particularly valuable in the everyday conduct of the newborn nursery giving as it does physiology, normal values and interpretation of abnormal findings. Part III deals with hereditary metabolic disorders, namely disorders of glycogen metabolism and hereditary galactose and fructose intolerance. Part IV deals with hypoglycemia in infancy beyond the newborn stage. It describes the general approach to the clinical problem, differential diagnosis, the biochemical tests available and their interpretation, and a rather complete differential diagnosis of individual hypoglycemic syndromes concludes this portion.

The final portion of the book is devoted to disorders of carbohydrate absorption and digestion concentrating particularly on specific enzyme deficiency states. An appendix includes special diets (galactose-free, sucrose and fructose free, leucine-restricted), and a table of carbohydrate content of foods. The bibliography is very complete and up-to-date. The book is lucidly written and it is highly recommended for medical students, house officers and all physicians who have to deal with newborns and young infants. This is a splendid opportunity to catch up in an important field which has had many recent advances.

* * *

PEDIATRIC THERAPY—Second Edition—Harry C. Shirkey, B.S. (Pharm.), M.D., F.A.A.P. (Editor), Director, The Children's Hospital of Birmingham, Ala.; Associate Professor of Pediatrics, Medical College of Alabama, Birmingham, Ala.; Professor and Chairman, Department of Pharmacology, Howard College, Birmingham, Ala.; member, Revision Committee, and Chairman, Pediatric Panel, Pharmacopeia of the United States. The C. V. Mosby Company, St. Louis, Mo., 1966. 1223 pages, $18.50.

Dr. Shirkey, Director of Childrens Hospital at Birmingham, Alabama, aims to give a sophisticated and detailed presentation of treatment, from pharmacologic principles to complete practical management of sick children. It is more than a text of applied clinical pharmacology in that it attempts to deal with all aspects of therapeutic management.

The first three parts (chapters 1 to 32) are of a general nature: part one on drug therapy, including fundamentals of drug therapy, techniques of administration, conditions which alter dosage, principles in choice of drugs, teratology, reactions, etc.; part II, general therapy, includes chapters on home therapy, chronically ill children, parenteral fluid, nutritional and gamma globulin therapy, to list a few. There is also a series of chapters on symptomatic treatment.

The remainder of the book is divided into categorical arrangements of diseases (respiratory, cardiovascular, genitourinary, metabolic, allergic, infectious, tumors, poisonings, etc.). Within each category are several chapters detailing the management of children with specific diseases and, at the end, a table of drug dosages. Throughout, there is a liberal use of good illustrations.

Dr. Shirkey had the help of 83 other authors and, as might be predicted, the result is somewhat uneven. A few of the contributors fail in their assignment, most chapters are quite adequate, and several are very good and contain practical information which is not available in the usual texts.

This book will be most valuable to the practicing physician and will provide a quick brush-up on the details of management learned as a house officer, particularly of less common diseases. Even if these is not entire agreement with the recommended handling of all of the features of a particular illness, it will serve as a reminder and be a check on the physician's own program of management. Generally, he will also acquire some useful new information.

This book will be a useful addition to the clinician's library if he does not already have the first edition, which came out in 1964.

Roderic H. Phibbs, M.D.

* * *

PRINCIPLES OF PATHOLOGY—Second Edition—Howard C. Hopps, M.D., Chief, Division of Geographic Pathology, The Armed Forces Institute of Pathology. Appleton-Century-Crofts, New York, N.Y., 1964. 403 pages, $8.95.

This volume is the second edition of *Principles of Pathology* first published by Hopps in 1959. According to the author, the book was written primarily for the undergraduate medical student and, as the title indicates, stresses basic concepts in pathology rather than detailed factual information. The approach is a classical one, beginning with circulatory disturbances and degenerative processes and proceeding through metabolic and nutritional disorders, inflammation, infection, regeneration and repair, and neoplasia. Rather than writing a synopsis of pathology, Hopps has emphasized causative mechanisms and broad concepts of the effects of disease. The style of the 12 chapters is lecture-like. The writing is clear and engagingly interesting. The illustrations are unusual in a book on pathology in that they consist of black-and-white line drawings, tables, diagrams, formulas, and graphs—the sort of visual material that good teachers often employ to illustrate their lectures. This book would not replace one of the standard textbooks of pathology for today's medical student, but ought to be useful to him in organizing his basic knowledge in the subject.

* * *

BECK'S OBSTETRICAL PRACTICE—Eighth Edition—E. Stewart Taylor, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado. The Williams & Wilkins Company, Baltimore, Md., 1966. 658 pages, $14.50.

E. Stewart Taylor has completely rewritten the eighth edition of Beck's famed textbook and, with his revision, has reduced the 1,115 pages of the seventh edition to 658 pages in the current one. Inasmuch as there are now 15 American textbooks of general obstetrics in print, each new book brings forth speculation as to which portion of the limited market each author hopes to appeal. Dr. Taylor has clearly set his sights on the medical student.

The book is well suited to the student beginning his obstetrical clerkship, for within the early portions of the book there is sufficient information to enable the student to intelligently participate in normal antenatal care and deliveries. The chapters "Chronologic development of pregnancy," "Changes in maternal organism," and "Multiple pregnancy" are superb for their organization, presentation of general principles, and relevance. The book is profusely illustrated, using much of the material from previous editions.

The author's tendency to mention all subjects, no matter how rare, leads in a book of this small size to somewhat superficial and dogmatic discussion in many areas. The comments on uterine inertia are particularly brief. It is also difficult to understand why in a book of this type, so much space is given to topics such as version and inversion of the uterus. An additional topic that should be of great interest, but has been apparently deleted from all the current obstetric textbooks, would be a discussion of normal values of laboratory tests for each trimester of pregnancy and the postpartum period.

The portions of the book which should have widespread appeal are the bibliographies found at the end of each of the 49 chapters. These are current and well chosen, and by themselves are worth the price of the book. The book is highly recommended for all students of obstetrics, regardless of their state of training.

Robert C. Goodlin, M.D.

* * *

SYNOPSIS OF OBSTETRICS—Seventh Edition—Charles E. McLennan, M.D., Professor of Gynecology and Obstetrics, Stanford University School of Medicine, Palo Alto, Calif. The C. V. Mosby Company, St. Louis, 1966. 471 pages, $6.85.

The Synopsis has been used profitably by many generations of medical students and house officers. The Seventh Edition is another good one and should be of great help to students of the subject. The volume is decidedly readable and surprisingly broad in its coverage for a synopsis. Dr. McLennan again demonstrates a knack for positivism when the facts warrant it and caution when they do not. The volume is a fine guide to labor and delivery but also includes discussions of the many medical and surgical complications of pregnancy and of fetal and maternal physiology. The illustrations in the present edition have been up-dated from the old and are excellent. In point of fact this is almost the only major change from the prior edition; the chapter headings are identical, and in most cases the text is altered only in minor ways. This does not detract from the usefulness of the volume, however. It should serve as a valuable, quick reference for those who lack either the time or inclination to consult one of the larger texts.

Leo D. Lagasse, M.D.

* * *

PEDIATRIC ELECTROCARDIOGRAPHY—Normal and Abnormal Patterns, Incorporating the Vector Approach—Warren G. Guntheroth, M.D., Associate Professor of Pediatrics, University of Washington School of Medicine, Seattle. Illustrated by the Author. W. B. Saunders Company, Philadelphia, Pa., 1965. 150 pages, $7.00.

The author's stated purpose in this 138 page monograph is to provide an accurate but brief introduction to electrocardiography with emphasis on pediatric experience. He succeeds in doing just that.

In addition to the standard tables on the range of normal R, S, and R/S voltage ratios published by Ziegler in 1951 and Manning and Smiley in 1964, the author gives examples from 110 normal patients of all ages from his files, as well as illustrating the features of abnormal tracings from his files of patients with known cardiac lesions. The first half of the text is a review of electrophysiology summarizing general principles, lead systems, vector analysis, methods of recording and routine interpretation of the ECG and VCG. There follows a brief review of disorders of rate and rhythm and examples of the variations of the normal ECG at all ages with the normal evolution of the adult vector pattern.

Throughout the text specific examples are cited from patients with known anatomic lesions. Both the ECG and VCG taken with the Frank system are presented in each case and the component vector forces analyzed.

In the section on hypertrophy the author struggles against the loose use of such terms as hypertrophy, diastolic overload, pressure work and volume work as they apply to ventricular hypertrophy in a variety of congenital and acquired lesions. He presents both the characteristic changes in vector forces and voltage criteria for right, left and combined ventricular and atrial hypertrophy. There follows a large section on disorders of the sequence of excitation in which the author describes the characteristic patterns and vector analysis of the bundle branch blocks, pre-excitation, myocardial infarction, endocardial cushion defects and single ventricle. Special attention is given to the right ventricular conduction defects which are of particular importance in the pediatric population. Finally, there is a short chapter on disorders of repolarization, the presumed mechanisms and the clinical conditions in which these disorders are encountered.

The monograph is brief and simple. All statements are well documented and reenforced with references to the recent pertinent literature; a list of 120 references is appended. The book serves as an easily readable review of the highlights of electrocardiography as they apply to pediatrics for students and housestaff with some prior knowledge of the field.

* * *

CLINICAL OBSTETRICS AND GYNECOLOGY—Volume 9, Number 1: Radiology in Obstetrics—Edited by Alvin M. Siegler, M.D., D.Sc.; and Diseases of the Breast, edited by George C. Escher, M.D. Hoeber Medical Division (Harper & Row, Publishers, Inc.), New York, 1966. Published quarterly, $18.00 per year, by subscription only; about 1,200 pages per year.

These two subjects are reviewed with great completeness by the several authors. The approach to the uses of radiology in obstetrics is up to date and for the most part enlightened. Appropriately the first monograph discusses the hazards of radiation to mother and fetus. The importance of this topic can hardly be over-emphasized and the treatment by the authors is both readable and pertinent. The sections on The Use of Radioactive Isotopes for Placental Localization and New Frontiers in Obstetric Radiology, are both thorough, thoughtful, and up-to-date discussions of the state of the various arts and will be of interest both to practitioners and workers in the field. The discussion on isotopes by Hibbard is surprisingly complete and up-to-date. Many of the latest advances in this fast-growing field are discussed. The reviews of the Soft Tissue Techniques for Placental Localization and Hysterosalpingography are satisfactory but these subjects are well reviewed elsewhere. The importance of antenatal radiographic study of the fetus is somewhat over-emphasized and some of the material is presented with considerably more conviction than the facts may warrant. In general the section on Radiology in Obstetrics is helpful, informative, and up-to-date.

The symposium on the breast is a brief but valuable collection of short monographs dealing with subjects of interest to any physician who sees women patients. The discussion on common benign lesions of the female breast is of value chiefly because it should help one to distinguish benign from malignant lesions of the breast. Perhaps the most informative and pertinent treatise is the one on mammography. The uses and limitations of this technique are nicely presented. Other topics in the symposium on the breast include chemotherapy, radiation therapy, and the evaluation of newer techniques in the treatment of breast cancer. While each topic is well enough handled it would be of greatest interest to those who treat breast cancer. In summary, the symposium on the breast is well presented and readable and should be of interest to all who see female patients.

LEO D. LAGASSE, M.D.

SURGERY—Principles and Practice—Third Edition—Carl A. Moyer, M.D., Bixby Professor of Surgery, Washington University School of Medicine, St. Louis; Jonathan E. Rhoads, M.D., D.Sc. (Mel.), John Rhea Barton, Professor of Surgery, School of Medicine, Professor of Surgery, Graduate School of Medicine, University of Pennsylvania, Philadelphia; J. Garrott Allen, M.D., Professor of Surgery, Stanford University Medical School; Attending Surgeon, Stanford-Palo Alto Hospital; and Henry N. Harkins, M.D., Ph.D., Professor of Surgery, University of Washington School of Medicine, Seattle. J. B. Lippincott Company, Philadelphia, Pa., 1965. 1828 pages, $18.00.

In the first edition of this surgical textbook, the authors stated that their intent was to try to satisfy the need for a basic text which combines physiologic, biochemical, pathologic and anatomic bases. Their aim was not to try to include all surgical conditions, but to present the more common problems and their treatment.

The authors have created a clear and practical textbook of value not only to the medical student, but to the intern, resident and practitioner. The usefulness of this book is enhanced by the frequent revisions. It is somewhat confusing, however, that the authors rotate the order of their names with each edition, but this is designed to maintain the concept of a single work of the four men. The authors have written about half the text and assigned the remainder to other specialists in specific fields.

This new edition has been brought up-to-date with minor revisions in some areas and major changes in others. New chapters have been added on Tumors of the Head and Neck and the Mathematical Analysis of Surgical Data. The chapter on Operative Surgical Care has been rewritten by James D. Hardy, M.D. An entire chapter is devoted to Portal Hypertension. A new section on Cold Injury has been added to the chapter on Burns. Other new sections include: Abnormal Bleeding in the Surgical Patient, Hereditary Factors in Cancer, Spinal and Epidural Anesthesia, and Hemobilia. Most other areas have also been brought up-to-date.

In general, this book is current, practical and a most valuable basic text.

ROBERT S. OZERAN, M.D.

* * *

LUPUS ERYTHEMATOSUS—A Review of the Current Status of Discoid and Systemic Lupus Erythematosus and Their Variants—Edited by Edmund L. Dubois, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Director of the "Collagen Disease" Clinic, The Los Angeles County General Hospital, Los Angeles, Calif. McGraw-Hill Book Company (The Blakiston Division), New York, 1966. 479 pages, $27.50.

This is a new and impressive work on lupus erythematosus. The editor, Edmund Dubois, has personally managed over 500 patients with lupus erythematosus at the Los Angeles County Hospital. The book is comprised of 16 chapters, seven written by 14 guest contributors and nine written by Dr. Dubois. It reviews with success the recent progress in our understanding of this disease.

The first chapter written by John Talbot aptly discusses the historical background of lupus erythematosus. Until recently all studies were descriptive. The discovery of the "LE" cell by Hargraves, the most important event in the history of lupus, gave impetus to studies of pathopysiology and the concept of autoimmunity. The pathology of lupus erythematosus is thoroughly discussed by Bruce Cruckshank. The diagnostic importance of fibrinoid deposition and presence of hematozylin-stained bodies are particularly emphasized. Victor Pollak and Conrad Pirani next review their experience with the natural history and therapy of the renal lesion. These authors believe that lupus nephropathy, which is usually of grave significance, can be most benefitted by maximal doses of steroids. The chapters on autoimmune aspects by Dr. Ian Mackay and immunologic phenomenon by Peter Miescher are superb and bring the most current etiologic concepts into the test. In the later chapter, the various immunological abnormalities encountered in systemic lupus are described. The diagnostic and biological significance of the immune reactions against the cell nucleus and its constituents are thoroughly discussed.

The remainder of the book is a clinical review of lupus erythematosus as observed by the editor. Chapters on the LE cell test and patient management particularly reflect the authors' extensive clinical experience and are classics. Sections of the book discussing the occurrence of avascular bone necrosis, gangrene of the extremities, and vasculitis in lupus erythematosus are particularly rewarding.

One possible criticism is that the authors' concept of lupus erythematosus is broader than most. Controversial subjects such as lupoid hepatitis, specificity of the LE cell test, the relationship of discoid and systemic lupus, the relationship of systemic lupus and rheumatoid arthritis, and drug associated lupus erythematosus are covered basically by describing the authors' viewpoint. However, these are primarily arguments only of terminology.

The book is a very comprehensive monograph. The detailed bibliography consists of 1,453 references and the subject index is quite complete. The paper and printing are excellent. It is beautifully illustrated, many of the illustrations being in full color. The book is recommended to anyone interested in lupus erythematosus and is certainly the most authoritative text available.

Denny L. Tuffanelli, M.D.

* * *

SHOCK AND HYPOTENSION—Pathogenesis and Treatment—The Twelfth Hahnemann Symposium, edited by Lewis C. Mills, M.D., Professor of Medicine and Head, Section of Endocrinology; and John H. Moyer, M.D., Professor and Chairman, Department of Medicine, both of Hahnemann Medical College and Hospital, Philadelphia, Pa. Grune & Stratton, Inc., New York, 1965. 718 pages, $29.00.

The stated purpose of this symposium is (1) to bring together the foremost investigators in the field of shock to exchange ideas, to unify concepts and to stimulate further investigation and (2) to present the current knowledge on shock in a manner suitable for up to date clinical application in the community. One hundred and thirty physicians and Ph.D.'s participated in this 718 page volume, representing the experts from the well known "shock" centers all over the country.

Following the keynote address by Dr. Jacob Fine on the current status of the problem of traumatic shock, the papers are organized under the following headings: (1) basic normal vascular physiology and pharmacology, (2) physiological and biochemical alterations in shock, (3) hemorrhage and hypovolemic shock, endotoxin and exotoxin shock, cardiogenic and miscellaneous shock, (4) irreversible shock and (5) special therapeutic procedures. As in previous Hahnemann Symposia each group of three or four papers is concluded by a panel discussion.

In the first section on normal vascular physiology, the regulation of cardiac output, peripheral, cerebral, renal and muscle blood flow are discussed as well as the relationship of the microcirculation to shock. The hemodynamic and metabolic effects of shock in different organ systems are then outlined, followed by a discussion of the role of catecholamines, renin and angiotensin. Under the different types of shock the authors present experimental work to clarify the mechanisms and hemodynamics as well as methods of management in each instance. The section on therapy discusses the uses of low molecular Dextran, hypothermia, hyperbaric oxygen and aldosterone in modifying shock.

The book presents a tremendous amount of information including both observations from painstakingly performed individual animal experiments and the clinical application of general principles thus derived in humans. The extensive and detailed presentation of the experimental work and observations result in successful achievement of the first aim of the symposium—that of presentation of data and exchange of ideas. The serious student can find collected in one volume the ideas of the experts in the field, and pertinent experimental work and references on the subject as of the date of the syposium. As a guide and aid to the practicing physician in the management of clinical problems the volume is less successful. It is too long, too detailed, and too expensive to serve as a handbook for ready clinical application.

* * *

PREVENTIVE MEDICINE FOR THE DOCTOR IN HIS COMMUNITY—Third Edition—An Epidemiologic Approach—Hugh Rodman Leavell, M.D., Dr. P.H., Professor Emeritus of Public Health Practice, Harvard School of Public Health; Consultant on Health, Ford Foundation (India); and E. Gurney Clark, M.D., Dr. P.H., Professor of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine, Columbia University; and 23 contributors. McGraw-Hill Book Company (The Blakiston Division), New York, 1965. 684 pages, $12.50.

The third edition of this widely used textbook is significantly improved over its predecessors. Not only have factual materials been brought up to date, but nearly every chapter has been revised in the light of rapid advances in medical science and the changing concepts of the roles of community health agencies. The names of three of the former contributors have disappeared from the list; there are seven new ones among the total of 23. The chapter on epidemiology has been expanded by about 20 pages of description and examples of the use of the epidemiologic approach in scientific research. Although the application of epidemiology to problem-solving in a local, current situation has not been made explicit, it can readily be derived. The reviewer knows of no clearer, step-by-step description of the analysis of an epidemiologic problem.

The greatest merit of this book is its clinical approach to community health. A disease problem is defined, its special characteristics are identified, and these characteristics are made the basis for the rational development of a program for the reduction of mortality and morbidity. With the ever-increasing interaction of public health, public hospital, and voluntary hospital agencies with medical practitioners and their organizations, the application of this kind of rational planning becomes imperative, if we are to preserve the best elements of medical practice as it has been known in the past, and to assure that medical care of the future will be improved, not merely made more accessible to more people. Although this edition was written too soon to include a specific discussion of Public Law 89-97 ("Medicare"), there is a good summary of the historical background against which the new legislation developed and a sound review of the principles to be considered in the implementation of this and other health care legislation. Those who aspire to leadership in organized medicine would do well to study this book. The style is direct and forceful; the type-setting and printing are good; the format is graceful; the binding is sound.

Rodney R. Beard, M.D.

PHARMACOLOGY AND PATIENT CARE—Second Edition—Solomon Garb, M.D., Associate Professor of Pharmacology, University of Missouri School of Medicine; and Betty Jean Crim, R.N., M.Ed., Assistant Professor of Nursing, University of Missouri School of Nursing. Springer Publishing Company, Inc., New York, 1966. 469 pages, $4.75 (flexible cover). (Also available hardbound for $6.25.)

As indicated by its title, this book is more than a pocket pharmacology text for nurses. It consists of three sections, I—General Considerations, II—Pharmacology of Drug Groups, and III—Use of Drugs in the Care of Patients. Section I contains definitions, instructions for drug administration, much useful information of a general nature, and a stern warning about the dangers of narcotics. This chapter places too much emphasis on physical dependence as the cause of drug abuse, doesn't mention spree use and fails to point out that drugs have persistent desirable cerebral effects for some people. Section II consists of brief but generally accurate descriptive pharmacology supplemented by adequate lists of references. Section III is therapeutics from the nurse's point of view with emphasis on pharmaco-therapy and nursing care.

This book is "bare bones" as a text for a pharmacology course but could profitably be placed in hospital libraries and at nursing stations for quick reference.

H. W. Elliott, M.D.

* * *

RADIOLOGIC DIAGNOSIS IN INFANTS AND CHILDREN—Armand E. Brodeur, M.D., M.Rd., F.A.C.R., Chief Radiologist, Cardinal Glennon Memorial Hospital for Children, St. Louis, Mo.; Associate Professor of Radiology and Associate Dean, St. Louis University School of Medicine, St. Louis, Mo.; Medical Director, School of X-ray Technology, St. Louis University, St. Louis, Mo. The C. V. Mosby Company, St. Louis, 1965. 503 pages, $26.50.

This book is very well done, it is easily readable and fulfills its goal of teaching the basic approach to pediatric radiologic diagnosis. It is beautifully illustrated and has examples of most of the common conditions encountered in pediatric radiology. The book is well organized and it is quite helpful in pointing out the common pitfalls for most conditions. It is not comprehensive enough to be of great value to pediatric radiologists, but the author intended it predominantly for residents in radiology. The book actually goes beyond that and is of value also to radiologists who examine some pediatric cases in their practice. The first chapter, outlining the approach to the technique of differential diagnosis in pediatric radiology, is going to be quite valuable to the beginner. The organization into the sections of the head and neck, the thorax, abdomen, skeleton and integument is along the traditional lines of treatment of the subject. The addition of a chapter on the mistreated child syndrome, in the fifth section, undoubtedly represented a problem for the author, as he felt it to be important enough to be separate and this is probably why he didn't include it in the chapter on the skeleton.

Illustrations are plentiful and of good technical quality. The lesions are well seen and arrows pointing to them are abundant. The captions are short and to the point.

One weakness of the book is that the references are not correlated to the text and therefore lose a great deal of their usefulness.

The book is highly recommended as an introduction to pediatric radiology for beginning residents and as a short refresher source on the subject for those who do little pediatric radiology.

Alexander R. Margulis, M.D.

CIBA FOUNDATION STUDY GROUP NO. 21—HASHISH: Its chemistry and pharmacology—in honour of Professor Dr. G. Joachimoglu; Edited by G. E. W. Wolstenholme, O.B.E., F.R.C.P., F.I.Biol., and Julie Knight, B.A. Little, Brown and Company, Boston, 1965. 96 pages, $2.95.

This little book of 96 pages offers much information for pharmacologists, toxicologists and medical practitioners interested in keeping up to date on the scientific and medical aspects of Cannabis sativa, without necessarily becoming experts in the field. It is composed not only of the papers of the principal participants in the Ciba Symposium, but also of the extemporaneous discussion by both principal and secondary participants. Among the participants are Herman Blaschko and Edith Bülbring of Oxford University, G. Joachimoglu of Athens and member of the Drug Supervisory Board of the United Nations, A. D. Macdonald of the University of Manchester, and Eleanor Zaimis of the Royal Free Hospital of London. The United States was represented by Nathan B. Eddy of the National Institutes of Health. There is still much confusion concerning the effects on experimental animals and man because of the lack of standard preparations, methods of extraction of active principles and methods of administration. Thus the effects of smoking hashish and ingestion of the resinous bhang or charas are somewhat different. There is a detailed paper on the isolation of various principles obtained by column and thin layer chromatography, with structural formulas of five such compounds. Several speakers were of the opinion that tetrahydrocannabinol is the true active principle, but this opinion was not universally accepted. There was also a discussion of whether the use of cannabis leads to true addiction or simply to habitual use. There was an attempt to characterize the psychological make-up which leads to use of cannabis, and of the chronic psychological and physical results.

Clinton H. Thienes, M.D.

* * *

PHARMACOLOGY AND THERAPEUTICS—Sixth Edition—A Textbook for Students and Practitioners of Medicine and Its Allied Professions—Arthur Grollman, Ph.D., M.D., F.A.C.P., Professor and Chairman of the Department of Experimental Medicine, The Southwestern Medical School, The University of Texas; Attending Physician, Parkland Memorial Hospital; Consultant in Internal Medicine, Baylor University Hospital. With the collaboration of Evelyn Frances Grollman, A.B., M.D., Member of the House Staff of the Bellevue Division, Columbia University College of Physicians and Surgeons; Ensign (R), United States Public Health Service. Lea & Febiger, Philadelphia, 1965. 1,181 pages, $15.00.

A textbook which is revised approximately every two years should meet the demands of those who require an up-to-date discussion. This can truly be said to describe the Sixth Edition of Grollman's Pharmacology and Therapeutics. In my review of the Fifth Edition I wrote: "This latest edition . . . is as sound and up-to-date and complete as such a book can be and stay in the practical price range." The statement can be repeated for this Sixth Edition which ends the era for a one-man complete textbook in pharmacology, since it is the handiwork of two Grollmans. In their preface, the authors emphasize that they have written not only for the student studying pharmacology for the first time, but also for the student in his clinical years and later as intern, resident and practitioner.

Each succeeding edition of this textbook, as is true of most textbooks going through several revisions, adds new drugs, and sometimes drops old ones whose use has been superseded by new ones. The Grollmans have accomplished this with but a slight increase in the size of the book. The Fifth Edition contains 1,070 text pages, the Sixth 1,114 pages. The indexes of the Fifth Edition contain 60 pages of index, the Sixth 64 pages.

Although the general arrangement of the book has not been changed, there was a shift in the positions of Gastrointestinal Drugs, Renal Drugs and Cancer Chemotherapy Drugs to more logical arrangements.

Although throughout, the discussions are scholarly and show the hand of the experienced scientist and writer, the discussion of antihypertensive drugs and of the adrenal corticoids stand out as the product of one who has spent his academic life in research in these fields.

Formulas for chemical structure have been changed in the light of new information (e.g., colchicine); the treatment of acute barbiturate poisoning, new concepts of neuro-hormone action, new psychomotor stimulants, iron and other topics have been restated. An appendix on Classification According to Therapeutic Use has been dropped.

As one interested in Toxicology, this reviewer would like to see an expansion of the toxicological discussions in this popular and important book, especially since toxicology is given so little time in the medical school curriculum. More descriptions of pathological changes due to overdose would be helpful to the reader.

CLINTON H. THIENES, M.D.

* * *

MANAGEMENT OF EMOTIONAL PROBLEMS OF CHILDREN AND ADOLESCENTS—A. H. Chapman, M.D., Associate Clinical Professor of Psychiatry, University of Kansas School of Medicine; Attending Psychiatrist, St. Mary's Hospital, Menorah Medical Center, and Research Hospital, Kansas City, Missouri. J. B. Lippincott Company, Philadelphia, Pa., 1965. 315 pages, $9.50.

Dr. Chapman's book is an ambitious compilation, reminiscent of general texts offering to cover material that can't be dealt with except briefly and lightly in the scope of one book.

The author takes you on a long, fast-moving journey, traveling chiefly on middle ground and not allowing you to view much of the scenery at any point. After the trip one has the impression little new was offered. The frames of reference vary from religious and moralistic (pages 6, 8) to the common sense school of psychiatry, with hints and dribbles of Freudian psychology. In general the author plays safe and takes everyone's views into consideration, recommending referral and medication freely.

The book attempts to cover the "entire range of emotional health and sickness in children and adolescents." There is information of a variety—from acne to schizophrenia and love to ulcerative colitis. Although it is entitled "Management of Emotional Problems . . ." the book is more a "guide to emotional disorders" as referred to in the preface. There is little actual direction for the clinician unless he is naive and inexperienced; the direction is perhaps more for the medical student, lay person, or unsophisticated parent. The contents are too skimpy for use as a psychiatric text.

Part I smacks of lectures to the lay public more than material presented to physicians. It includes outlines and directions for parents raising children: how to do things, such as "love your children"; how to deal with masturbation; when to tell the adopted child the facts; and so forth.

The author offers much that psychiatrists can take to task. His answers are a bit pat and euphemistic. For example, one wonders after reading Part I where the author tells the parents to love their children, how the parents go about it if they are not already loving them. Parts II, III and IV are in a different vein and aimed primarily as medical information, probably for the general practitioner. They include touching on an assortment of psychiatric information, deleting—as far as I can tell—only the problems of smoking and narcissism.

The author tends to deal with schizophrenia by vacillating, leaving issues unclear, tending to minimize the illness in childhood, glossing over the severity in adolescence, and being optimistic as to prognosis in treatment (pages 290, 296, 297).

More bibliographic references are needed, e.g., on "school phobias," schizophrenia, etc. The book seemingly tries to be a psychiatric Spock and to offer reassurance for the anxiety of the physician in dealing with the emotionally disturbed young.

MARION STEELE, M.D.

* * *

CURRENT PSYCHIATRIC THERAPIES, Vol. VI—1966 —An Annual Publication—Edited by Jules H. Masserman, M.D., Professor and Co-chairman of Psychiatry, Northwestern University, Chicago, Illinois. Grune & Stratton, Inc., New York, N.Y., 1966. 382 pages, $13.50.

This volume consists of a series of 52 articles arranged in seven parts: Rationale of Treatment; Childhood and Adolescence; Adult Psychotherapy; Group Psychotherapy; Physical Therapies; Community Psychiatry; and Institutional Therapy.

The articles range in length from very brief to moderate, two to 14 pages: They vary equivalently in quality and no doubt in their significance to the reader, who is almost certain to find here something to please and something to annoy. The overall idea seems to be to provide a mixture of brief survey and short encounters with a goodly number of the various aspects of current psychiatric treatment. It does not pretend to be an encyclopedia but as a sort of *Reader's Digest* type Annual, it will give most readers an introduction to at least one or two subjects that they would be unlikely to find in their usual reading. Recommended for this purpose.

* * *

VITREORETINAL PATHOLOGY AND SURGERY IN RETINAL DETACHMENT—Paul A. Cibis, M.D., Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Missouri. 293 pages, $20.00.

This informative book by the late Paul Cibis is the most complete text on this rapidly changing field to date.

The first of two parts entitled Vitreoretinal Pathology in Retinal Detachment is divided into the normal vitreous experimental observations, basic and clinical concepts, and clinical observations.

Part II entitled Vitreoretinal Surgery in Retinal Detachment is concerned with surgical techniques, histopathology of enucleated eyes, and comments and summary. Dr. Cibis includes the latest cryosurgical and lazer techniques including their known complications.

Unfortunately, Dr. Cibis died before his radically new intravitreal techniques could be thoroughly evaluated. Although many ophthalmic surgeons will disagree with Dr. Cibis' ideas and techniques, he has produced enough new concepts to keep a number of ophthalmologists busy for years evaluating them.

This book is highly recommended as a reference text and as a personal "must" for anyone doing retinal detachment surgery.

R. M. SINSKEY, M.D.

"son pouvoir antiémétique est élevé"*

Vomiting:
In Geneva they have a word for it

In Geneva, too, Dramamine is a familiar word. Like physicians the world over, they know that "its antiemetic potency* is high" ("son pouvoir antiémétique est élevé").

Nausea and vomiting caused by infection or simple functional gastrointestinal disturbances are quickly controlled by this classic antinauseant.

Usual Adult Dosage: One or two tablets every four hours as needed.

Precautions: Dramamine, notably nontoxic itself, may mask the symptoms of streptomycin toxicity. Patients should be cautioned against operating automobiles or dangerous machinery because of possible drowsiness.

*Neyroud, M.: Praxis 44:648-650 (July 14) 1955.

Research in the Service of Medicine SEARLE

relied on round the world ■
Dramamine®
brand of
dimenhydrinate
classic antinauseant
Ampuls (for intramuscular or intravenous use)
Supposicones® / Liquid / Tablets

Birth Control Information For Welfare Patients

Many women who desperately want and need birth control information often cannot get it—simply because welfare agencies refuse to provide this service.

This indictment of "second-class medical care" for welfare patients is contained in a signed editorial in a recent issue of the *Journal of the American Medical Association*. The editorial was prepared and signed by John C. Ballin, Ph.D., secretary to the AMA Committee on Human Reproduction.

"Women able to afford a private physician can get adequate information on methods of fertility control as well as the actual contraceptive supplies. They assume the right to these services as part of first-rate medical care," Dr. Ballin writes.

"Yet, the indigent woman who must go to public health and welfare agencies is all too often discriminated against by being denied these services which she so desperately needs and wants. This is second-class medical care at best."

There are several reasons, says Dr. Ballin. In some cases, birth control services are prohibited in tax-supported health facilities by statute, or are omitted from the programs.

In other cases, physicians and public health officials lack the courage to break an unwritten rule against mentioning birth control.

"Whatever the cause," writes Dr. Ballin, "the net result is that impoverished women continue to have babies that they do not want and cannot support, either psychologically or financially."

All over the world, individuals and groups have endorsed the principle of responsible parenthood, Dr. Ballin points out. In 1964 the AMA House of Delegates stated that "An intelligent recognition of the problems that relate to human reproduction, including the need for population control, is more than a matter of responsible parenthood; it is a matter of responsible medical practice."

The AMA also has stated as a matter of official policy that "the prescription of child-spacing measures should be made available to all patients who require them, consistent with their creed and mores, whether they obtain their medical care through private physicians or tax- or community-supported health services."

Most major legal barriers to dissemination of birth control information have now been removed in this country, Dr. Ballin notes. A 1965 decision of the U.S. Supreme Court declared unconstitutional a Connecticut ban on the use of contraceptives. In May of this year the Massachusetts legislature repealed a state law prohibiting the sale or dissemination of information on contraceptives.

In addition, the AMA House of Delegates has urged that appropriate legislation be enacted, wherever necessary, so that physicians can legally give contraceptive information to patients.

Thus, Dr. Ballin appeals to physicians, public health workers, and municipal authorities to "show greater courage in breaking down the barriers to provide birth control services in all public health and welfare programs and in municipal hospitals."

"This is not, or should not be, a religious issue," he says. "It is, instead, a matter of giving first-class medical service to all our citizens. Certainly in a country which prides itself on having the world's finest system of medical care, we can no longer afford to deny this integral part of comprehensive health care to the very segment of our population that needs it most."

Your public relations problem has been our prime consideration in collection procedures during two generations of ethical service to the Medical Profession.

*

THE DOCTORS BUSINESS BUREAU

Since 1916

821 MARKET ST., SAN FRANCISCO 94103
GArfield 1-0460

Finer **ALLERGENIC EXTRACTS**

- *specialized allergy service*
- *diagnostic and therapeutic extracts*

PROMPT • PERSONAL SERVICE

Frees you from details and delays.
Provides you with ready-to-use extracts.

Descriptive literature sent on request.

BERKELEY BIOLOGICALS

Second & Hearst Sts., Berkeley, Calif. 94710
2275 W. Lincoln Ave., Anaheim, Calif. 92801

For topical treatment of DENUDED and PAINFUL SKIN LESIONS

Anti-Pyrexol antiseptic ointment reduces pain, minimizes scarring, aids healing of burns, sunburn, scalds, lesions, wounds, and local inflammation of skin and mucous membrane. Sold through surgical supply houses. 1, 5, 10 and 50 lb. tins. Time tested—professionally since 1921. Active ingredients: Oils of spearmint, bay, wintergreen (syn.), salicylic acid, lanolin, zinc oxide, phenol .44%, ortho-hydroxyphenyl-mercuric chloride .056%, petrolatum, paraffin.

Anti-Pyrexol Benzocaine. Acutely anesthetic. Contains Benzocaine 3%. 1, 5 and 10 lb. tins.

EASY SPREADING
Anti-Pyrexol
KIP, INC.—LOS ANGELES 21

OFFICERS
OF THE CALIFORNIA MEDICAL ASSOCIATION

(Continued from Page 5)

COUNCIL COMMITTEES

Finance Committee

Harold Kay, Oakland (Chmn.)
Roger C. Isenhour, San Diego
Frank C. Melone, Ontario
Joseph W. Telford, San Diego
Malcolm C. Todd, Long Beach

Committee on Legislation

Dan O. Kilroy, Sacramento (Chmn.)
Stuart C. Knox, Los Angeles
Harold E. Wilkins, Downey
John Rumsey, San Diego
Samuel R. Sherman, San Francisco

Advisory Board to Woman's Auxiliary

James C. MacLaggan, San Diego (Chmn.)
John G. Morrison, San Leandro
William Quinn, Los Angeles
Carl E. Anderson, Santa Rosa
Eugene Hoffman, Los Angeles

Benevolence Fund Operating Committee

Clyde L. Boice, Palo Alto (Chmn.)
Alexander Fraser, San Francisco
Elizabeth Mason Hohl, Los Angeles
Don C. Musser, San Francisco
George Wolf, Fresno
Dudley M. Cobb, Jr., Los Angeles

Public Health Service Issues New Research Grants Index

The Public Health Service has published a fifth edition of the *Research Grants Index,* an annual publication containing scientific subject matter summaries of more than 17,000 research projects supported by the PHS during fiscal year 1965.

The 2,432-page Index is printed in two volumes. The first volume classifies research grants and contracts according to scientific subject headings in alphabetical order, covering more than 5,500 aspects of biomedical research. Volume II contains three sections. The first lists the projects in numerical order of the grant numbers, showing investigators' names, addresses, project titles and recent publications. The second section lists grants by 75 broad scientific areas, and the third is an alphabetical list of investigators.

The *Index,* first issued for fiscal year 1961, enables scientists to identify other researchers in their own and related fields and to exchange information before research results appear in journal sources. The publication is produced by the Research Documentation Section, Division of Research Grants, National Institutes of Health, and is distributed to libraries of all PHS-grantee institutions.

The two-volume *Research Grants Index* (PHS Publication No. 925) is available to the public from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., at $13.75 for the set.

THE BLUE CHIP
STOCK
In Generic Pharmaceuticals

Towne
ASSURANCE
OF OPTIMUM
CLINICAL
EFFECTIVENESS

Pharmacies everywhere now stock TOWNE generic pharmaceuticals. Prescribe TOWNE to assure your patients of consistent high quality and uniformity ...at sensible prices.

PARTIAL LIST OF PRODUCTS

DIOCTYL SODIUM SULFOSUCCINATE N.F.
(S.G. capsules; 100mg—250mg)
HEPARIN INJECTION
(10M—20M—40M USP Units/cc)
C. T. MEPROBAMATE N.F.
(200mg—400mg)
C. T. PENICILLIN G USP
(200M—250M—400M Units)
C. T. PREDNISONE USP
(2.5mg—5mg)
C. T. QUINIDINE USP
(3 gr.)
C. T. RESERPINE USP
(0.1mg—0.25mg—1mg)
TETRACYCLINE HCL USP
(H.S. capsules—250mg—Domestic material)

Product List available on request.

Towne PRESCRIPTION PRODUCTS DIVISION

Towne, Paulsen & Company, Inc.
Pharmaceutical Chemists Monrovia, California

Saxon

Physician's Wife Helps Build Diabetic Camp

There's a forest growing in Geauga County, Ohio, that a physician's wife helped plant.

In the July issue of *MD's Wife* magazine, Mrs. Henry B. John tells how she and her husband helped turn this area into the world's first permanent camp for diabetic children.

With a few helpers, Dr. and Mrs. John planted by hand more than 25,000 pine seedlings in the early 1930's. Today, some of the trees are more than 80 feet tall. They form the shelter for a camp that houses more than 50 children.

"A diabetic child," said Dr. John, "needs many things—open air, mixing with other diabetic children to realize that he is not alone, and medical adjustment. It is not enough to keep him alive. He needs to be taught how to live."

Though a controlled diabetic (one whose blood sugar does not remain above normal levels more than six hours in 24) is capable of every physical and mental achievement of the normal child, some diabetic children lack initiative because they fear insulin reactions.

At the camp, these children are shown that there is no limit to activity, because activity helps burn up sugar normally and reduces the necessary insulin dosage.

The camp is administered by a board of trustees and is supported by private donations and contributions from the Diabetes Association of Greater Cleveland and other civic groups and foundations. Less than one-third of the operating cost is realized from camper fees. Fees are determined by the family's ability to pay.

Dr. Henry John was medical director for 15 years until 1948. Mrs. John was camp activities director for 18 years, and has helped to train staffs for camps in Greece, Holland and Canada, as well as the United States.

In 1930 the camp was one building and a couple of tents. Today, it has rustic, permanent buildings, including a Great Hall, dispensary, bath houses, diet kitchen, handicrafts shop and sleeping cabins. The 85 acres also contain a swimming pool, tennis courts, archery lanes, a baseball diamond, and activity buildings.

Except for medical and dietetical care, camp life is normal, with the usual sports and recreational activities. The only out-of-the-ordinary activity is "Insulin Parade" every morning before breakfast, when nurses administer each child's prescribed dose of insulin. Every camper's food is carefully weighed and checked.

"If he can realize that in every other way (except diet and the need for insulin) he is no different from others, the diabetic child is well on the way to pursuing a normal course of living," Mrs. John said.

The name of the camp is Ho Mita Koda, which in the Sioux language means "welcome my friend." More than 2,500 diabetic children have enjoyed the camp's facilities in the past 30 years.

MD's Wife, the magazine in which the article appears, is a publication of the Woman's Auxiliary to the American Medical Association, Inc.

Your public relations problem has been our prime consideration in collection procedures during two generations of ethical service to the Medical Profession.

THE DOCTORS BUSINESS BUREAU
Since 1916
821 MARKET ST., SAN FRANCISCO 94103
GArfield 1-0460

Economical Long-term Therapy for Iron Deficiency Anemia

Tablets & Elixir

FAMOUS
Fergon®
brand of FERROUS GLUCONATE
C.M.A.P. CODE # 5261

BREON
BREON LABORATORIES INC.
Subsidiary of Sterling Drug Inc.
90 Park Avenue, New York, N.Y. 10016

How long will it take her to recover from her hip fracture if she just doesn't care?

of a modern corticosteroid economy of hydrocortisone

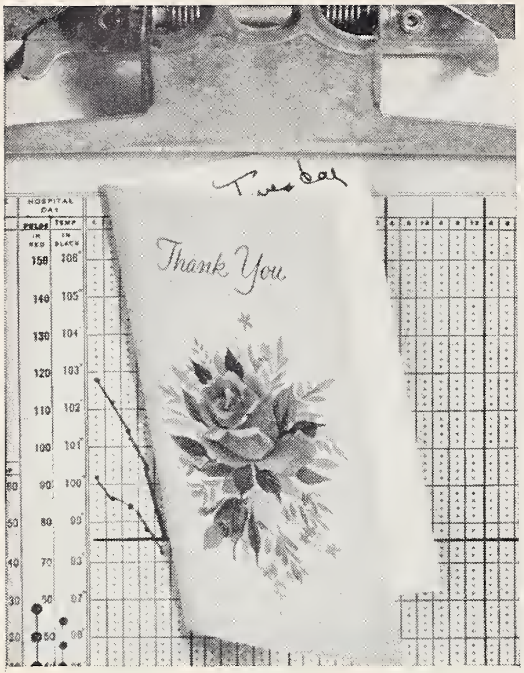
Now…a choice of 3 economical sizes

120 Gm. jar 15 Gm. tube 45 Gm. tube

fluocinolone acetonide — an original steroid from

SYNTEX

LABORATORIES INC., PALO ALTO, CALIF.



DID YOU EVER GET A "THANK YOU" NOTE FROM A SPECIAL-DIET PATIENT?

It can happen. Send for our free booklet and see the remarkable things that can be done with a diet that is built on Cream of RICE.

It's called "How To Make A Special Diet Taste Extra Special!" You'll find delicious recipes for bland, wheat-free, milk-free, egg-free and low-salt diets.

A recent research study compared the breakdown of Cream of RICE with oat, wheat, corn and barley cereals and concluded that Cream of RICE was easiest to digest.

Cream of RICE is fortified with Vitamin B_1, Riboflavin, Niacin and Iron. And it's low in residue and fat. The patient gets dietary protection, flavor satisfaction and good nutrition. And you may actually get a "Thank you."

ADVERTISED IN Reader's Digest

15½ million families (26 million worldwide) buy each issue.

CREAM OF RICE, Box CA 10, West Chester, Pa. 19380

Please send_______(state number desired) free copies of "How To Make A Special Diet Taste Extra Special!" to

Name____________________

Address____________________

City____________________

State____________Zip Code__________

Appendicitis Hazardous For the Elderly

For those over 60, acute appendicitis can be a special threat.

An elderly person's diseased appendix tends to perforate easily, often leading to serious complications from infection. Elderly death rates are much higher than average for appendicitis, otherwise considered a routine ailment.

Prompt exploratory surgery is the best way to counteract this threat, says an article in the September 5 *Journal of the American Medical Association.* For a variety of reasons, many elderly appendicitis victims are not operated upon soon enough, the authors say.

Twenty-eight consecutive cases of acute appendicitis in patients aged 60 to 91 were reviewed by the authors, two physicians at Peter Bent Brigham Hospital and the Veterans Administration Hospital, West Roxbury, Mass.

They found the appendix had perforated in 17 of 21 patients operated upon more than 24 hours after the first symptoms of illness. Only one of six patients suffered a ruptured appendix when operated upon less than 24 hours after the onset of symptoms.

A striking reduction in the death rate was noted (2 of 28 patients, or 7 per cent), compared to a 28 per cent death rate among elderly appendicitis victims studied 30 years earlier at Peter Bent Brigham Hospital.

Part of the reduction is apparently due to antibiotics now available, and partly due to improved patient care, the authors said. Thirty years ago, there was a "remarkably high" rate of appendix perforation (82 per cent in the study cited). This was most likely due to delaying of surgery, the authors said.

The classical symptoms of appendicitis, such as nausea, vomiting, and a steady pain in the lower right section of the abdomen, were present in more than half of the elderly patients in the current study. Details of medical treatment are about the same as those for younger people, the report said.

Older people sometimes put off seeking treatment, the authors pointed out. Many live alone, removed from friends and relatives who might otherwise urge them to seek medical advice. Still others have fixed ideas about the diagnosis of their illness, and even about the proper way to treat it.

All these things add to the hazards of appendicitis when it strikes the elderly.

Physicians can reduce illness and death by remaining alert for appendicitis symptoms, and "by recommending urgent surgical exploration when appendicitis is first suspected," the report said.

The authors are Arnold G. Coran, M.D., and H. Brownell Wheeler, M.D.

Medical Science Examining Palms

The old-fashioned "palm readers" were right, after all: a person's future can be foretold to some extent in the lines and creases of his hand.

Medical science, however — not superstitious guessing—is doing the modern palm reading.

Heart disease and other birth defects are among health problems now being studied by examining an infant's palm and foot prints. Two articles in the August 29 *Journal of the American Medical Association* describe progress in the comparatively new science of dermatoglyphics, the study of skin patterns.

These crease patterns form during the first three months of pregnancy, and remain unchanged throughout an infant's life. The palm prints of most normal, healthy babies are similar; variations from these normal patterns may give clues to disease and its cause.

There is good evidence that many rubella-damaged infants can be identified at birth by palm-print examination, say two University of Minnesota investigators in one *Journal* report. They found significant alterations in the palm prints of 28 rubella-damaged infants.

It may never be possible, however, to use dermatoglyphics to identify rubella-damaged infants before birth. Even normal palm and foot prints vary widely, the investigators point out, and examination of a fetus is difficult. Only when there are other symptoms of rubella damage can dermatoglyphics be used to reinforce a suspicion of rubella damage, they said.

The authors are Milton Alter, M.D., and Robert Schulenberg, of the Division of Neurology, University of Minnesota, Minneapolis.

In a second *Journal* report, two Japanese physicians add further evidence that palm prints can be used to determine the general cause of heart disease.

Among Japanese patients with heart murmurs, the investigators found a significantly greater number of palm-print abnormalities among those with congenital heart disease than among persons who acquired heart disease after birth. These findings agree with results of earlier studies of Caucasian and Negro patients.

Thus, unusual palm prints may have a close relationship to genetic disease, the authors suggest. They said much more might be learned about congenital heart disease if a patient's family background were studied, using his relatives' palm prints as a guide.

The authors, Tsunekazu Takashima, M.D., of Yodogawa Christian Hospital, Osaka, and Susumu Yorifuji, M.D., of Kobe University School of Medicine, Kobe, studied 1,312 pairs of palm prints of Japanese and Caucasians. Among 44 patients with congenital heart disease they found

(Continued on Page 33)

The discomforts of

DIARRHEA
MUCOUS COLITIS
DIVERTICULITIS
SPASTIC URETERITIS
BLADDER SPASM

are relieved by
direct musculotropic action
with.....

Trocinate®
BRAND THIPHENAMIL HCl

Available in 100 milligram pink sugar-coated tablets.

The high therapeutic index permits dosage sufficient to relieve spasm promptly.

Administer 4 tablets every 4 hours until relief is constant, then adjust maintenance dosage.

Trocinate *BRAND* THIPHENAMIL HCl

Directly relaxes smooth muscle spasm
Combats hypermotility
Non-mydriatic, may be used in glaucoma

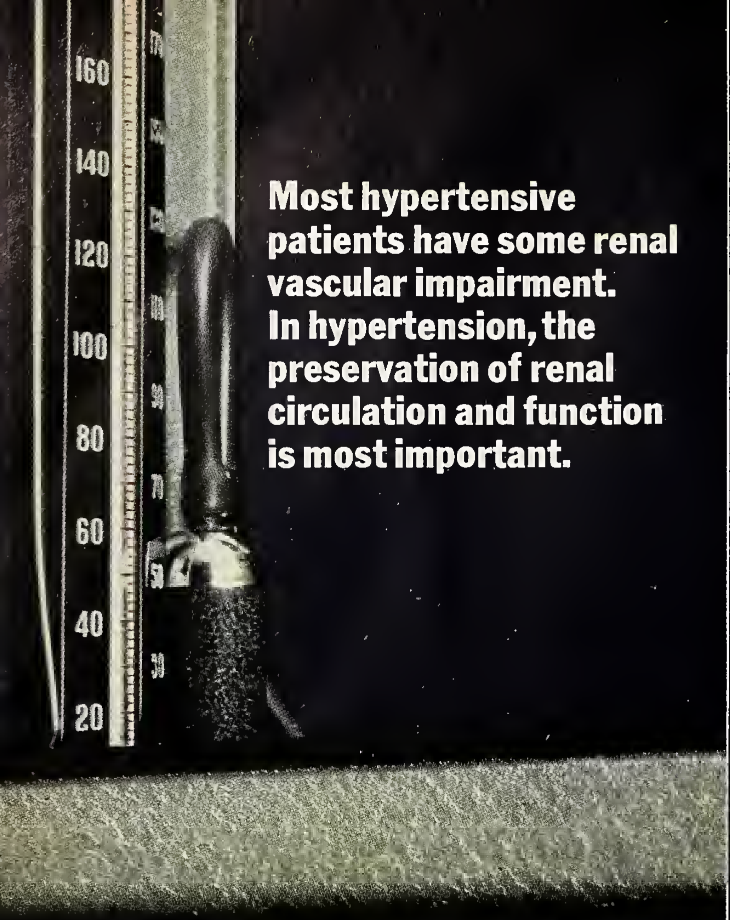
Sixteen years of clinical use, with absence of untoward effects, has established the safety and effectiveness of Trocinate.

Trocinate is metabolized in the body and completely eliminated, which is a safety factor. Dosage must be sufficient to maintain the therapeutic blood level.

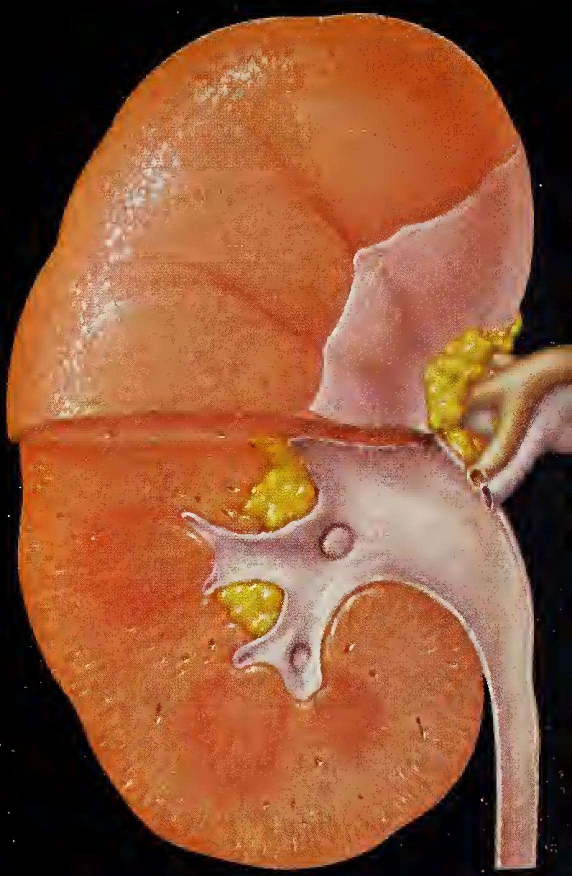
DISPENSED IN BOTTLES OF
100, 250 AND 2000 TABLETS

Literature and samples sent upon request

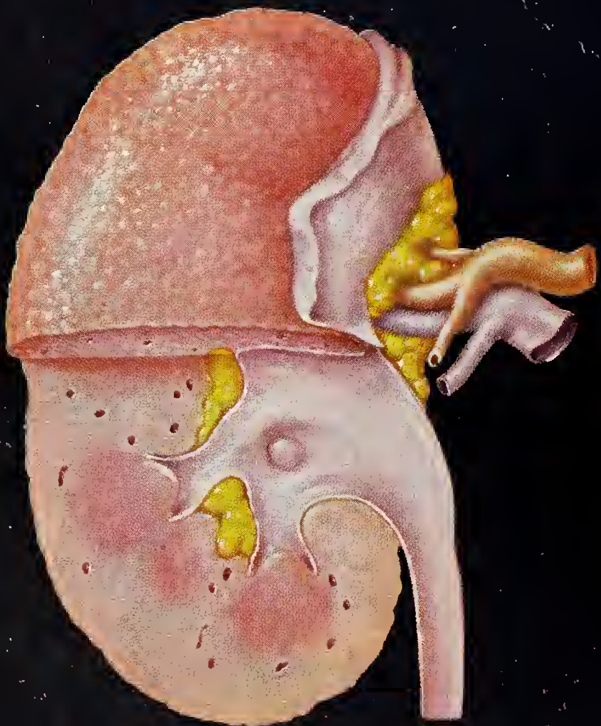
WM. P. POYTHRESS & CO., INC.
RICHMOND, VIRGINIA
Manufacturers of ethical pharmaceuticals since 1856



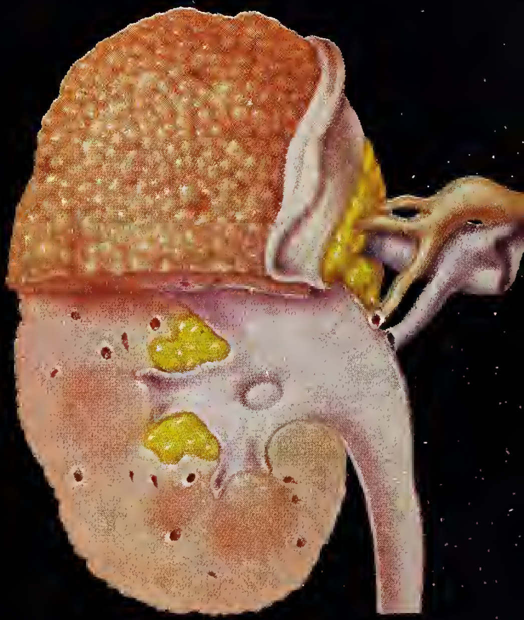
Most hypertensive patients have some renal vascular impairment. In hypertension, the preservation of renal circulation and function is most important.



1. minimal renal involvement associated with diastolic hypertension



2. moderate renal involvement associated with diastolic hypertension



3. advanced renal involvement associated with diastolic hypertension

Medical Science Examining Palms

(Continued from Page 17)

that 64 per cent had palm-print abnormalities, compared to only 17 per cent of 362 patients with acquired disease.

The medical knowledge to be gained by a careful study of skin patterns has no relation, however, to the "age-old seamy practice of palmistry," said a *Journal* editorial.

Though not a product of false science, dermatoglyphics did not entirely escape pseudo-scientific influences. One that clung to it for some time is the concept of "mongolism."

First described 100 years ago, the syndrome of "mongolian idiocy" became associated with finger and palm analysis. Later, an elaborate theory was developed to "prove" that mongolian races had a simian palm crease, and thus were somehow inferior to Caucasians.

"Although this prevalence (of a simian hand crease) has since been refuted by several investigators, the concept of 'mongolism' persisted for a long time, to the detriment of medical dermatoglyphics," the editorial said.

A sidelight of the report by the two Japanese physicians is that it revealed "no significant difference in palm prints" between Caucasians and Japanese, the editorial said.

Virus Diseases' Effects on Pregnancy

The relationship of premature birth to a mother's virus diseases during pregnancy, such as mumps, chickenpox, hepatitis, measles, and German measles (rubella), are reported in the August 29 *Journal of the American Medical Association.*

The various diseases had somewhat different effects on unborn children, the large-scale survey shows. The study, done in New York City between 1957 and 1964, involved 1,652 mothers. Premature children of mothers infected with virus diseases were compared with the premature infants of mothers who did not have these diseases during pregnancy.

By far the most damaging virus disease is rubella, the study shows. It caused more premature births, more fetal deaths, and more birth defects than any of the other virus diseases.

Why the other diseases cause prematurity isn't entirely clear, the report said. Rubella is the only one known to infect the fetus itself. The damaging effects of mumps, hepatitis, measles, etc., may be due to the mother's high fever, metabolic changes, or toxic products produced during disease.

Increases in prematurity and infant deaths were limited to the early weeks of pregnancy in the case of rubella, and late in pregnancy for mothers who had hepatitis.

(Continued on Page 37)

THE BLUE CHIP
STOCK
In Generic Pharmaceuticals

Towne
ASSURANCE
OF OPTIMUM
CLINICAL
EFFECTIVENESS

Pharmacies everywhere now stock TOWNE generic pharmaceuticals. Prescribe TOWNE to assure your patients of consistent high quality and uniformity ...at sensible prices.

PARTIAL LIST OF PRODUCTS

DIOCTYL SODIUM SULFOSUCCINATE N.F.
(S.G. capsules: 100mg—250mg)
HEPARIN INJECTION
(10M—20M—40M USP Units/cc)
C. T. MEPROBAMATE N.F.
(200mg—400mg)
C. T. PENICILLIN G USP
(200M—250M—400M Units)
C. T. PREDNISONE USP
(2.5mg—5mg)
C. T. QUINIDINE USP
(3 gr.)
C. T. RESERPINE USP
(0.1mg—0.25mg—1mg)
TETRACYCLINE HCL USP
(H.S. capsules—250mg—Domestic material)

Product List available on request.

Towne PRESCRIPTION PRODUCTS DIVISION

Towne, Paulsen & Company, Inc.
Pharmaceutical Chemists Monrovia, California

Especially...

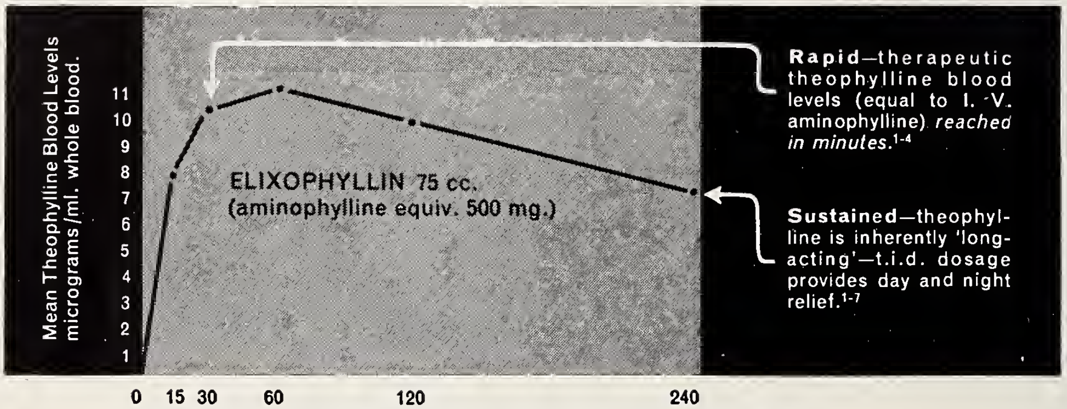
WHEN BRONCHIAL ASTHMA IS COMPLICATED BY HYPERTENSION • HEART DISEASE • HYPERTHYROIDISM

ELIXOPHYLLIN®

Each 15 cc. contains THEOPHYLLINE 80 mg.; ALCOHOL 3 cc.

...provides relief quickly, dependably, **safely.**[1-8]

...avoids the side effects and contraindications of ephedrine polypharmaceuticals or similar sympathomimetics



Rapid—therapeutic theophylline blood levels (equal to I. V. aminophylline) *reached in minutes.*[1-4]

Sustained—theophylline is inherently 'long-acting'—t.i.d. dosage provides day and night relief.[1-7]

Minutes after administration. Mean values in adult subjects following administration of the single dose commonly used in clinical practice.[8]

Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

Acute Attacks: single dose of 75 cc. for adults; 0.5 cc. per lb. of body weight for children.

24 Hour Control: for adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, first 6 doses 0.3 cc.—then 0.2 cc. per lb. of body weight as above. May be contraindicated in peptic ulcer and gout. Gastric distress rarely encountered.

References: (1) Kessler, F.: Connecticut S.M.J. *21*:205 (March) 1957. (2) Burbank, B.; Schluger, J., and McGinn, J.: Am. J. Med. Sci. *234*:28 (July) 1957. (3) Spielman, A.D.. Ann. Allergy *15*:270 (June) 1957. (4) Greenbaum, J.: Ann. Allergy *16*:312 (May-June) 1958. (5) Kessler, F.: Medical Times *87*:1298 (Oct.) 1959. (6) Bickerman, H.A., and Barach, A. L., in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, p. 516. (7) Wilhelm, R. E. in Conn., H. F.: Current Therapy—1961, Philadelphia, W. B. Saunders Company, p. 417. (8) Schluger, J. McGinn, J. T., and Hennessy, D. J.: Am. J. Med. Sci. *233*:296, 1957.

Sherman Laboratories
Detroit 11, Michigan

INDOCIN®
INDOMETHACIN

Indications: Chronic and acute rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout. **Contraindications:** Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy has not been established. Not recommended for pediatric age groups. **Warning:** Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism. **Precautions and Adverse Reactions:** Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum, carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity. Before prescribing or administering, read product circular with package or available on request.

Virus Diseases' Effects on Pregnancy

(Continued from Page 33)

In measles cases, ill effects were limited to prematurely born infants; measles did not cause a significant increase in fetal deaths.

On the other hand, when mothers had mumps, there was an increase in early-pregnancy fetal deaths, but few other complications. These early-pregnancy deaths may have been related to the effects the mumps virus has on the hormonal and placental changes that occur at this time, the authors said.

In chickenpox, there was no significant increase in early fetal deaths, stillbirths, or prematurity except in unusual cases.

Of mothers who had a virus disease in the first 12 weeks of pregnancy, 21.5 per cent gave birth to infants considered underweight. Only 4.4 per cent of those infected after the first 12 weeks of pregnancy had underweight babies.

Here are the survey's findings on each disease:

German measles (rubella)—Caused the greatest number of stillbirths, birth defects, premature births, and underweight births. Prematurity was limited to those mothers infected in the first 12 weeks of pregnancy.

Measles—A significant number of premature babies were delivered by mothers who had measles. The stage of pregnancy at which they contracted measles had little effect on prematurity.

Hepatitis—An increase in prematurity and infant mortality, but limited to mothers who had the disease late in pregnancy.

Chickenpox—Few complications, except in unusual cases.

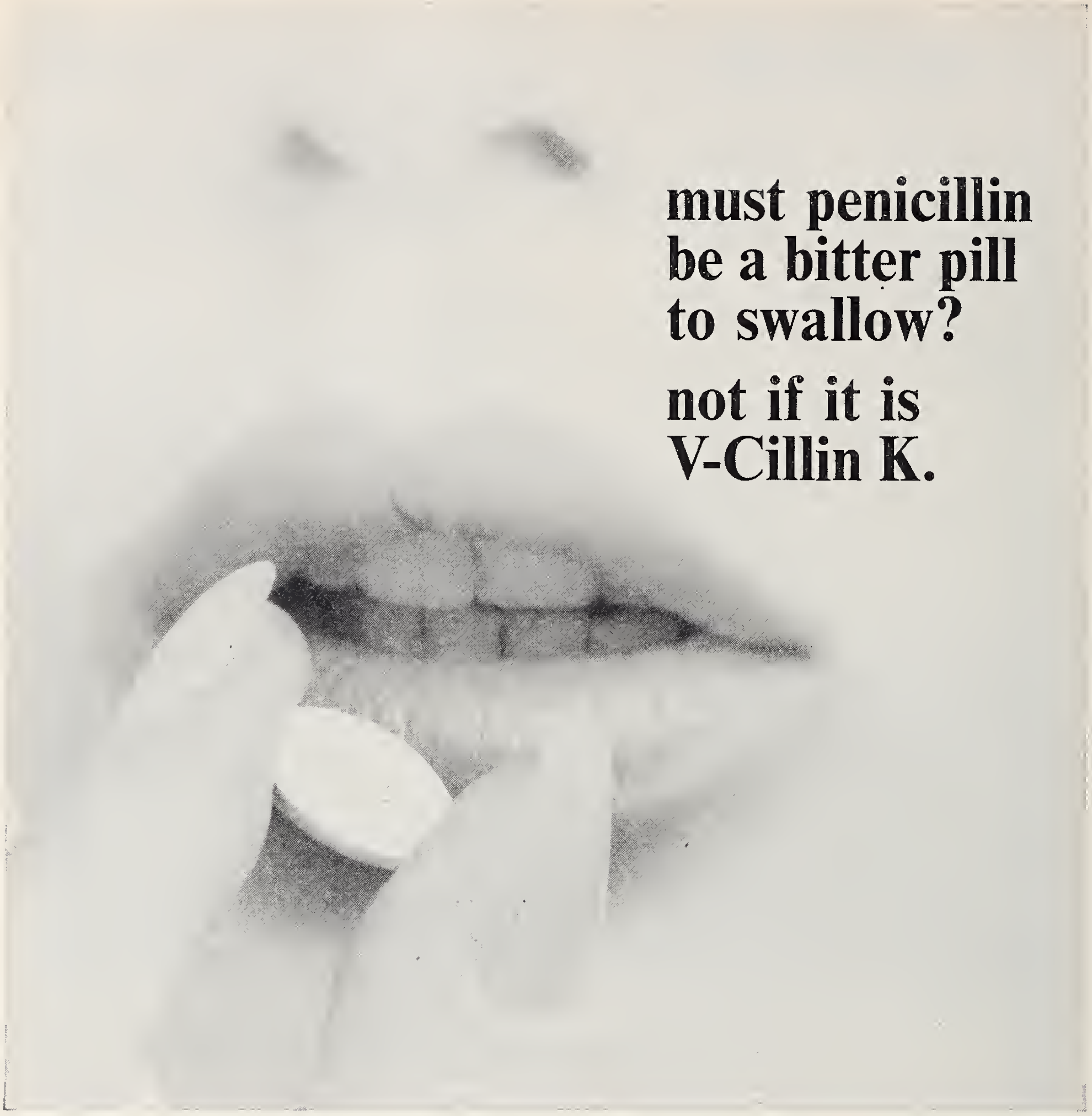
Mumps — Increase in early-pregnancy fetal deaths; few other ill effects.

The study of the relationship of birth defects and virus infections is still incomplete, pending hearing and mental-development tests when the children reach age five. Preliminary findings, however, indicate that only rubella causes a significant number of birth defects, and these are caused only if the mother is infected during the first 12 weeks of pregnancy.

Authors of the report are Morris Siegel, M.D., and Harold F. Fuerst, M.D., of the Department of Environmental Health Medicine and Community Health, State University of New York College of Medicine, and the Bureau of Preventable Disease, Department of Health, New York City.

MULTIPLE MYELOMA INVOLVING THE GASTROINTESTINAL TRACT—W. B. Goldstein and N. Poker (Rockefeller Institute, New York). Gastroenterology, 51:87-93 (July) 1966.

A case of multiple myeloma with extensive involvement of the stomach, duodenum, jejunum, and ileum is described. The lesions in the duodenum and small intestine were radiologically appparent during the patient's clinical course, although x-rays of the skeleton showed no pathological changes.



must penicillin be a bitter pill to swallow?
not if it is V-Cillin K.

V-Cillin K now has a unique glossy coating that banishes bitter penicillin taste and makes it easier to swallow. Within six seconds (just long enough for the tablet to get past the taste buds), the coating dissolves and the penicillin is ready for immediate absorption into the bloodstream. The patient still gets all the special benefits of V-Cillin K, including consistent dependability . . . even in the presence of food.

Indications: V-Cillin K is an antibiotic useful in the treatment of streptococcus, pneumococcus, and gonococcus infections and infections caused by sensitive strains of staphylococci.

Contraindications and Precautions: Although sensitivity reactions are much less common after oral than after parenteral administration, V-Cillin K should not be administered to patients with a history of allergy to penicillin. As with any antibiotic, observation for overgrowth of nonsusceptible organisms during treatment is important.

Usual Dosage Range: 125 mg. (200,000 units) three times a day to 250 mg. every four hours.

Supplied: Tablets V-Cillin K, 125 or 250 mg., and V-Cillin K, Pediatric, 125 mg. per 5-cc. teaspoonful, in 40, 80, and 150-cc.-size packages.

V-Cillin K® **Six-Second Barrier to Bitterness**

Potassium Phenoxymethyl Penicillin

601098

Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206.

Lilly

California
Medicine

REVIEW ARTICLE

Gout and Gouty Arthritis

Current Concepts and Management

EDWARD W. BOLAND, M.D., *Los Angeles*

GOUT IS AN ancient disease, probably the oldest medically recognized malady. Hippocrates wrote about it. Galen described tophi. Sydenham, Scudamore and Charcot gave classical accounts of the acute attacks. And Garrod, more than a hundred years ago, detected an excessive saturation of urates in blood of gouty victims.

Despite its antiquity and distinguished history, gout remained a neglected disease, both in clinical detection and investigative interest, until about 25 years ago. During recent years, however, significant advances have been made toward an understanding of its nature and in developing remarkably effective therapeutic measures for its control. Herein, an attempt will be made to summarize some of the advances that have influenced our current concepts of the disease and its practical management.

NATURE OF GOUT AND GOUTY ARTHRITIS

Gout is a genetically conditioned disorder of uric acid metabolism characterized by hyperuricemia, by the deposition of urate crystals in the tissue and by acute and chronic arthritis.

The exact incidence of gout is not known because the majority of persons with the inherited trait live normal spans of life without ever having clinical manifestations of the disease. A symptomatic hyperuricemia occurs in about 25 per cent of relatives of patients with gouty arthritis, but in only a few of these relatives eventually do overt signs of the disease ever develop. A clear distinction must be made between gout and gouty arthritis because only a fraction of those persons with persistent hyperuricemia ever have articular difficulties. Furthermore it should be emphasized that the finding of an elevated uric acid level may be entirely coincidental and that such elevations, transient or persistent, may be found in patients with other forms of rheumatic disorders, such as rheumatoid arthritis and osteoarthritis. The presence of hyperuricemia in a patient with arthritis does not necessarily mean that the joint disability is due to gout.

Gouty arthritis is by no means rare. Approximately 5 per cent of patients who attend arthritis clinics have the disease. Both gout and gouty arthritis have an overwhelming predilection for males. Roughly 95 per cent of cases occur in men. Certainly the burden of proof must be carried by the physician who makes the diagnosis of gouty arthritis in a female; and tophaceous gouty arthritis in a female is indeed a rarity. The condition respects neither race nor social level although the incidence of gouty arthritis is higher among men who are sufficiently affluent financially to indulge freely in provocatives of acute seizures.

The fundamental abnormal phenomenon in gout is hyperuricemia. The principal metabolic error producing this appears to be one of uric acid overproduction, but in some cases the crucial abnormality may consist of urate undersecretion. Investigations with radioactivity-tagged glycogen and with radioactive isotopes of substances incorporated into uric acid during its formation indicate

---

Reprint requests to: 2210 West Third Street, Los Angeles 90057.

that the rate of uric acid synthesis is accelerated in the majority of cases.

Excessive urate production appears to take place through two metabolic routes: (1) Endogenous biosynthesis from simple nitrogen and carbon precursors via shunt pathways that do not involve intermediate nucleic acid metabolism, and (2) excessive formation from preformed ingested nucleic acids or purines. The bulk of urate production results from endogenous synthesis, a fact that has practical therapeutic connotations since it explains why persistent hyperuricemia of substantial degree usually cannot be controlled by dietary restrictions alone.

The manifestations of chronic tophaceous gout are directly related to deranged uric acid metabolism. Clearly, they result from the supersaturation of urates in interstitial fluid and then their precipitation in such structures as joints, cartilage, bursae and renal parenchyma.

On the other hand, the pathogenesis of the acute bouts of gouty arthritis remains unsettled. In the past, urate metabolism was not considered to be involved, or, if so, only indirectly. The reasons were these: (1) Many persons with familial hyperuricemia, even though pronounced, remain asymptomatic throughout life, (2) the intravenous injection of uric acid with the production of blood levels as high as 20 mg per 100 ml does not precipitate a seizure, and (3) colchicine, which dramatically terminates most acute attacks, has no influence whatsoever on urate metabolism.

Several clues have prompted speculation that a temporary adrenocortical deficiency may be implicated in the development of acute seizures. Of the known provocatives of acute gouty arthritis, several, such as trauma, surgical operation, infection, allergic reaction, exposure to cold or heat, psychic upset and others, are stress-provoking conditions. These may produce sudden increases in adrenocortical hormone secretion and are followed by periods of decreased function, during which corticosteroids are lowered temporarily to subnormal levels. Because acute attacks are not likely to occur during stress, but rather three or four days later, they may have some relationship to depressed adrenocortical function. Such conjecture is strengthened by the fact that an episode may be relieved by the administration of adrenocortical steroids or corticotropin, and may be precipitated by the sudden withdrawal of either substance.

The popular hypothesis today is that the genesis of the acute attack depends on the fresh deposition of micro-urate crystals in the joint and that this is followed by the phagocytosis of the crystals during the ensuing inflammatory process. It is of interest that Garrod, more than a century ago, proposed that an acute attack was caused by formation of urates in the joint, but little consideration was given to his proposition. During the past few years, however, histologic evidence to support Garrod's concept has appeared. McCarty and Hollander[4] demonstrated some five years ago that urate crystals could be found in almost all gouty effusions, provided the aspirated material is viewed under the microscope with polarized light. Uniformly, such crystals are absent in the joint fluids of patients with non-gouty effusions, even when there is coincidental hyperuricemia of significant degree. Seegmiller, Howell and Malawista[7] then demonstrated that an inflammatory reaction, simulating acute gouty arthritis, could be produced regularly by injecting suspensions of microcrystalline sodium urate into the joints of gouty subjects. Furthermore, these reactions could be terminated rapidly by the intravenous administration of colchicine.

CLINICAL FEATURES

The natural history of classical gout may be divided into stages (Chart 1): In many patients with hereditary hyperuricemia signs of the disease never develop in the joints or elsewhere. Among those in whom symptoms do develop, the joint manifestations seldom appear before the age of 30 years, and more often they emerge during the fifth and sixth decades. The first clinical signs are usually those of recurrent acute arthritis. The pattern of the acute attack is distinctive and constitutes the most important criterion for diagnosis. It begins suddenly, progresses rapidly, is of relatively short duration and then retreats completely, without leaving joint residue. The frequency of occurrence in untreated cases varies with the severity. At the beginning, the bouts are characteristically separated by long, asymptomatic intervals of months or years. But later the tempo increases, bouts become more frequent and last longer (many days or weeks), and eventually recovery is not complete.

Finally, in progressive cases, the attacks are

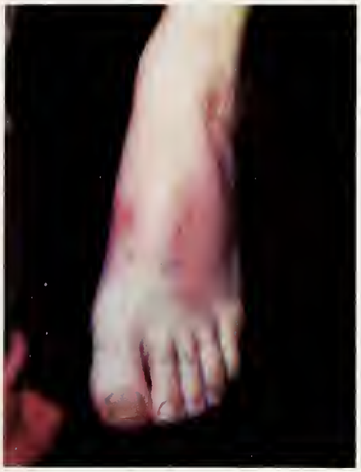


Figure 1.

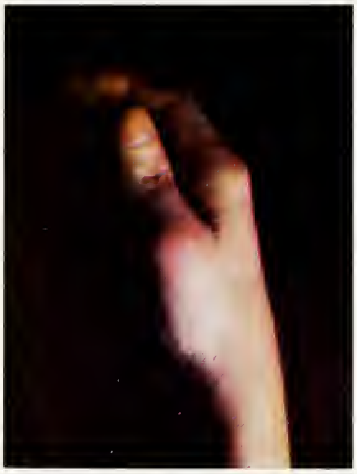


Figure 2.

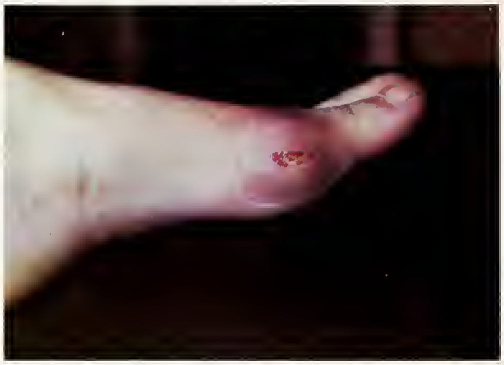


Figure 3.

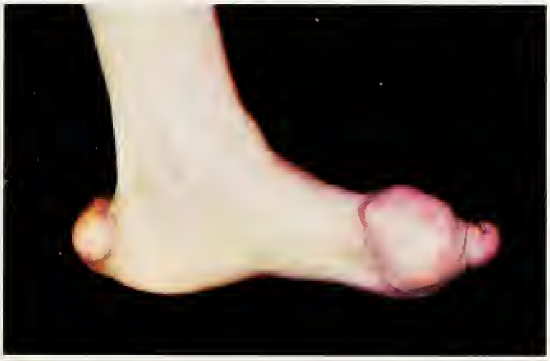


Figure 4.

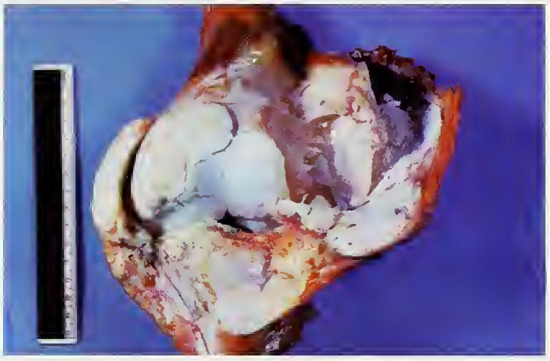


Figure 5.

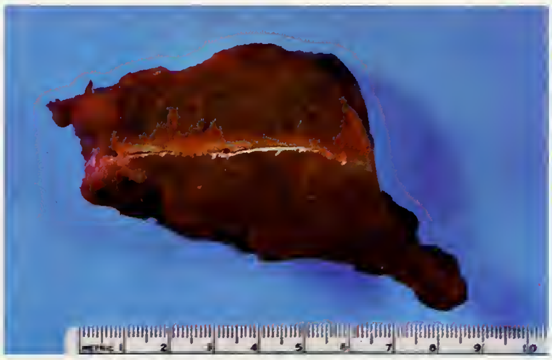


Figure 6.

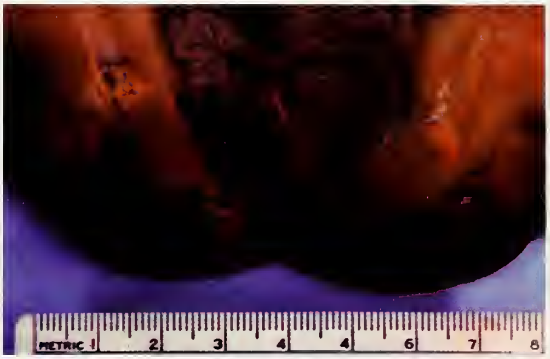


Figure 7.

Figure 1.—Acute gouty arthritis of tarsal joints.

Figure 2.—Episode of acute gouty arthritis involving metacarpophalangeal joint of thumb.

Figure 3.—Subsiding acute episode superimposed on chronic tophaceous gouty arthritis (see text).

Figure 4.—Advanced chronic tophaceous gouty arthritis.

Figure 5.—Knee joint filled with amorphous urates in severe chronic tophaceous gouty arthritis.

Figure 6.—Urates exuding from sacroiliac joint (see text).

Figure 7.—Chronic gouty nephropathy with urate deposits in pyramids.

followed by residual chronic symptoms and pathologic changes. Amorphous urates are deposited in the joints and other tissues and the stage of chronic gouty tophaceous arthritis is reached. Acute episodes are now superimposed on chronically involved joints. Uratic deposits may now have accumulated in subcutaneous, cartilaginous and renal tissues as well as in osseous and articular structures.

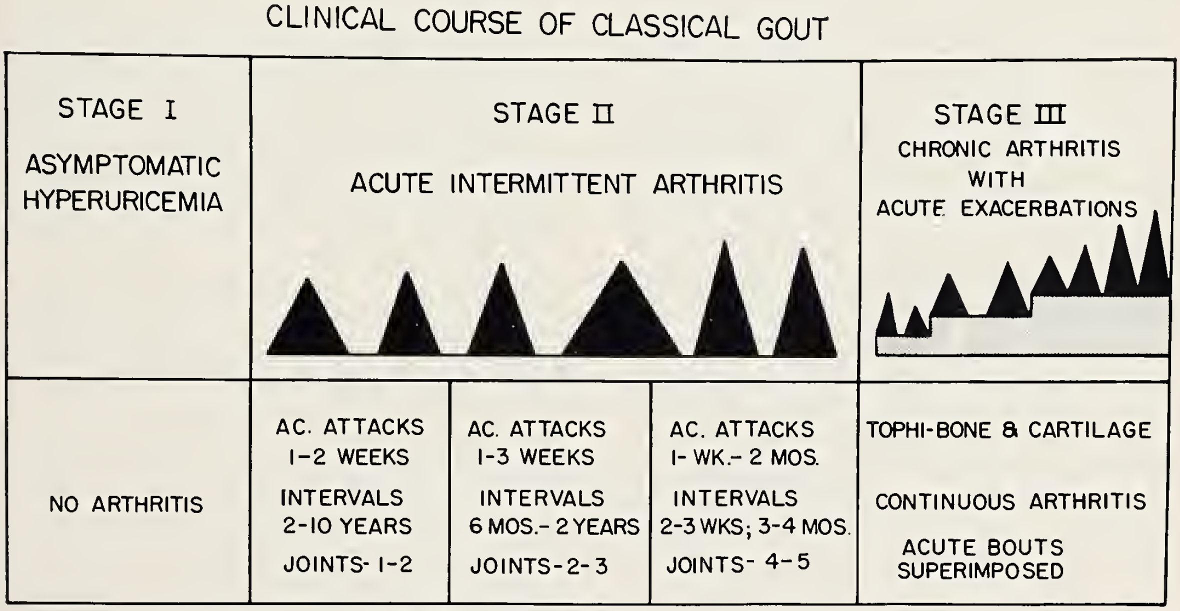
In the early phases, a single joint is involved, or at most two joints. Polyarthritis is rare. A bunion joint is affected at some time during the early attacks in about 65 per cent of cases, but any joint may be involved. Other favored sites include the tarsal joints (Figure 1), an ankle, knee, elbow or wrist.

The features of an acute attack are distinctive. The joint becomes sore, and within a few hours it is excruciatingly painful. The involved area is hot, swollen, dusky red and extremely tender. Early attacks, if untreated, generally last three to 14 days and then subside, but tenderness may persist for two to three weeks longer. Characteristically, complete resolution occurs, and the joint becomes normal in both function and appearance. The pattern: An acute, short-lived arthritis followed by complete restitution of function and then an asymptomatic interval. The repetition of these events—not the serum uric acid value—should be considered as the most important single criterion for diagnosis.

Acute gouty arthritis involving the metacarpophalangeal joint of the thumb is depicted in Figure 2. The joint was exquisitely painful, tender and hot. Two days after an intramuscular injection of phenylbutazone (1 gm) it appeared entirely normal. More than likely it would have responded similarly, though not as dramatically, to phenylbutazone or colchicine given orally in full dosage. This episode, like so many, began in the early morning hours. The patient was awakened with pain at three o'clock, and within a few hours the inflammatory signs were in full bloom.

A subsiding acute episode superimposed on chronic tophaceous arthritis of a bunion joint is shown in Figure 3. The referring physician misdiagnosed the condition as an infected bunion and incised the bursa. Urates were exuding from the lesion and there was desquamation of skin. The disease had progressed to a chronic stage with bursal and osseous tophi, but acute bouts still recurred.

In the advanced phases with osseous tophi, the joints become stiff, enlarged and deformed.



CLINICAL COURSE OF CLASSICAL GOUT

STAGE I ASYMPTOMATIC HYPERURICEMIA	STAGE II ACUTE INTERMITTENT ARTHRITIS			STAGE III CHRONIC ARTHRITIS WITH ACUTE EXACERBATIONS
NO ARTHRITIS	AC. ATTACKS 1-2 WEEKS INTERVALS 2-10 YEARS JOINTS- 1-2	AC. ATTACKS 1-3 WEEKS INTERVALS 6 MOS.- 2 YEARS JOINTS-2-3	AC. ATTACKS 1- WK.- 2 MOS. INTERVALS 2-3 WKS; 3-4 MOS. JOINTS- 4-5	TOPHI-BONE & CARTILAGE CONTINUOUS ARTHRITIS ACUTE BOUTS SUPERIMPOSED

Chart 1.—Natural history of classical gout. In many patients with hereditary hyperuricemia signs of the disease never develop in the joints or elsewhere and the disease does not extend beyond Stage I. When overt signs do develop (Stage II) the first clinical signs are usually those of recurrent acute arthritis. At first acute attacks last one or two weeks, affect one or two joints and are spaced two to ten years apart. In later phases of Stage II, bouts increase in frequency, last longer, involve more joints and are spaced at shorter intervals. In progressive cases there is a step-up of the attacks, and residual chronic symptoms and pathologic changes develop (Stage III). The joints are then chronically involved but acute episodes are superimposed.

Involved joints are sore, painful on weight bearing, and no longer is there freedom from discomfort between attacks. Huge osseous and articular tophi in chronic gouty arthritis are demonstrated in Figure 4. In some cases, tophi, even of this size, will disappear entirely after prolonged uricosuric therapy, or even more surely if the uricosuric agent is employed in conjunction with an xanthine-oxidase inhibitor, such as allopurinol.

The knee joint and the bursae of a patient with severe tophaceous gout who died of renal failure and came to autopsy is shown in Figure 5. These structures were literally filled with amorphous urates.

Erroneously, it was held for years that gouty arthritis never affects the spine, but an example of sacroiliac involvement with urates exuding from the joint is shown in Figure 6. In the same patient several small posterior intervertebral or apophyseal joints in the lumbar region also contained urates in abundance, findings that should abolish the notion that gout never affects spinal articulations.

Chronic gouty nephropathy is, of course, the most serious complication of gout. Uric acid stones or gravel occur in 10 to 15 per cent of patients at some time during the course of the disease. Nephropathy, with progressive impairment of renal function, was in the past responsible for about 15 per cent of deaths in patients with chronic tophaceous disease. Uratic deposits tend to obstruct the collecting tubules and produce an interstitial reaction resembling pyelonephritis, and the tubular obstruction may actually predispose to infection. Gouty nephropathy with uratic material deposited in the pyramids is depicted in Figure 7. It is assumed that the nephropathy of gout is caused by the deposition of urates resulting from an increased filtered load of uric acid by the kidneys. Therapeutically, this is an important consideration, especially now that agents capable of inhibiting the overproduction of urates are available. In patients with nephropathy, overproduction can be curtailed and it is not necessary to rely solely on chemicals that increase uric acid excretion.

TREATMENT

For physicians thoroughly familiar with the drugs now available, the management of gout and gouty arthritis is indeed a most gratifying medical experience. With the proper selection and use of drugs, and with close patient-physician cooperation, almost all cases of gout can be satisfactorily controlled. Like diabetes mellitus, gout varies in severity. The restrictions imposed and the medicines prescribed must be individualized, therefore, depending on the stage of the disease, its severity and extent, and the rapidity of its progress. Patients with infrequent acute attacks, interspersed with free periods lasting for many months or years, need little or no interval treatment. At the other extreme, dietary restrictions and uricosuric agents or xanthine-oxidase inhibitors are routinely indicated for patients with tophaceous gout. Treatment is not required for persons with asymptomatic hereditary hyperuricemia, but they should avoid obesity, purine-rich foods and the known provocatives of acute seizures. Today, the most common therapeutic sin —in contrast with that of 25 years ago—is one of commission, not omission. This consists in the indiscriminate treatment of a coincidental elevation of serum uric acid value. Today, the rheumatologist is too frequently faced with the necessity of undiagnosing gouty arthritis and of abandoning drugs and measures that have been prescribed without warrant on the basis of an elevated urate level alone.

Acute Gouty Arthritis

The treatment of acute gouty arthritis may be divided into two parts: Management of the seizure and the application of preventive measures during symptom-free intervals. Irrespective of the drug used, treatment should be started within a few hours of the onset of acute symptoms. The longer treatment is delayed, the more resistant and more prolonged is the episode.

Colchicine is a specific for acute gouty arthritis and remains the drug of choice of many physicians. When taken early and in full dosage, it will successfully terminate 85 to 90 per cent of attacks. The usual dosage is 0.06 mg every one or two hours until pain is relieved or until nausea or loose bowel movements, or both, ensue. The total dosage during any one course should not exceed 12 to 16 0.06 mg tablets. Frequently the tolerated and effective dose is quite constant and the patient often learns to stop the drug one or two tablets short of the amount that produces undesirable gastrointestinal symptoms. The response is usually dramatic, and within four to 12 hours the joint pain, redness and swelling and tenderness begin to subside. Pain may be completely relieved in one to three days. Maintenance doses—one or two 0.06 mg tablets a day—should be continued for at least two to three weeks in order to prevent recurrence. For patients who for one reason or another cannot take the drug orally, colchicine may be given intravenously. If the dosage by this route does not exceed 3 mg, gastrointestinal symptoms are usually obviated. It is customary to give a second intravenous dose of two or three mg after 12 or 24 hours.

During the past few years a number of colchicine analogues have been prepared and evaluated. Of these, desacetylmethylcolchicine and trimethylcolchicinic acid are effective for acute gouty episodes and have considerably less gastrointestinal toxicity. These drugs should not be considered as satisfactory alternative agents, however, because they may bring about other side effects such as tendency to produce agranulocytosis and loss of hair.

The mode of action of colchicine is not known. It does not counteract inflammation of any other type, and it has no effect whatsoever on uric acid formation or excretion. A newly postulated theory is that colchicine relieves gouty inflammation by diminishing or interrupting the phagocytosis of urate crystals, thereby breaking the cycle of inflammatory response to freshly deposited crystals.

Phenylbutazone (Butazolidin®) is, in my experience, the most effective drug for acute gouty arthritis. It is more reliable and certainly more agreeable than colchicine. Given early in an attack and in adequate dosage, it causes the pain of acute gouty arthritis to subside dramatically within a few hours (within 24 hours in 95 per cent of attacks), and the signs of inflammation usually resolve within 48 to 72 hours. In well established attacks, when the synovitis has existed for several days, the response is slower and may not be complete for a number of days.

The usual program for administering phenylbutazone orally for an acute episode is to prescribe a large initial dose of 400 to 600 mg, followed by 200 mg every two hours for two or three doses, so that a total of 1,000 mg is given during the first 24-hour period. Beginning on the second day and continuing until the inflammation has subsided, 100 mg three to four times a day is prescribed, the frequency depending on the severity of the attack and the response. Noxious side effects, which occur so commonly with full therapeutic doses of colchicine, are not a problem with phenylbutazone. An occasional patient experiences gastric irritation from large initial doses, and in such circumstances the drug may be administered intramuscularly. Given infrequently and for short periods, such as for an acute gouty attack, phenylbutazone rarely produces toxic reactions.

The response of acute gouty arthritis to phenylbutazone given intramuscularly in a single dose of 0.5 or 1.0 gm is dramatic, almost like a parlor trick. If given early, an attack frequently may be aborted within a few hours. The intramuscular material is very handy for an episode that follows surgical operation or occurs under circumstances which preclude the oral administration of drugs.

Indomethacin (Indocin®) has analgesic and anti-inflammatory effects in acute gouty arthritis. But, to obtain results, large amounts are needed, such as an initial dose of 200 to 300 mg, followed by three or four additional doses of 100 mg each on the first day. Then 200 to 400 mg a day is required for another three to four days. In general, the response is similar to that obtained with phenylbutazone, but it has not proved to be nearly as reliable. Furthermore, many patients are simply unable to tolerate the large doses that are required for relief. Effective dosage is all to often interrupted by the occurrence of such side effects as epigastric distress, nausea, headache or dizziness.

Adrenocorticotropic hormone (ACTH) given intravenously (20 units) or intramuscularly (30 to 40 units) is capable of rapidly suppressing an acute gouty seizure but may be followed by a so-called "withdrawal attack." A large intramuscular dose of a long-acting *corticosteroid analogue,* such as 40 to 60 mg of triamcinolone acetonide (Kenalog®) or methylprednisolone acetate (Depo-Medrol®), is often effective. In stubborn cases steroids may be used advantageously in conjunction with phenylbutazone. For a refractory attack, relief may be obtained by injecting the joint locally with a long-acting corticosteroid analogue. But, in general, corticosteroids and ACTH should be considered only as adjunctive measures, to be held in reserve for the occasional case in which response to phenylbutazone or colchicine is unsatisfactory.

Interval Management

During stage II there may be periods of months or years when the patient is free of all symptoms. The length of the periods varies with the severity of the disease, and the therapeutic measures recommended must vary accordingly. Management between attacks has two objectives: To prevent recurrences of acute episodes and to prevent chronic tophaceous changes. If the disease is mild and attacks occur no more often than every one or two years, and if they respond promptly to colchicine or phenylbutazone, then no therapy during the symptom-free periods is needed. Some experienced rheumatologists prescribe colchicine, 0.06 or 0.05 mg daily, as prophylaxis even against infrequent attacks, while others give the drug under special circumstances such as following trauma, infections, surgical operations or other stress. If attacks recur every few months, then daily maintenance doses of colchicine should be prescribed routinely.

Rigid dietary restriction is no longer necessary. The heavy ingestion of rich foods may increase urate levels and may serve as provocatives of an acute attack, but, except in mild cases, urate levels cannot be kept within normal range by dietary restrictions alone. The gouty subject synthesizes uric acid endogenously from simple chemical units of his own fat, carbohydrate and protein. Nowadays patients are asked to avoid high purine foods such as liver, kidneys, sweetbreads, sardines, anchovies, tongue and the like. Meat is usually allowed once or twice a day, depending on the severity of disease, and alcohol is usually permitted in moderate amounts.

Urate diuretic drugs are initiated under the following circumstances: (1) In all subjects with gouty arthritis who are under the age of 30 years, (2) when tophi, whether subcutaneous, osseous, cartilaginous or visceral, are present, (3) when acute attacks continue to recur frequently in spite of prophylactic doses of colchicine.

Chronic Tophaceous Gout

With the drugs now available the vast majority of patients with chronic tophaceous gout can be treated successfully. The goals of therapy are: (1) To control chronic arthritic symptoms by reducing the size of existing osseous and articular tophi, (2) to prevent or reduce the frequency of superimposed acute attacks, and (3) to prevent or decrease the tendency toward urate deposition.

Maintenance doses of colchicine (0.06 mg once or twice daily) should be given routinely in an effort to diminish the occurrence rate of acute seizures. Such doses, which are well tolerated over periods of years, should be a part of basic management and should be used in conjunction with urate diuretics when these are indicated.

Uricosuric drugs act by increasing the urinary excretion of urates, producing a state of negative urate balance and reducing the total body pool of urates, including tophaceous deposits. To be effective these drugs must be given uninterruptedly for protracted periods, perhaps for the remainder of the patient's life.

Probenecid (Benemid®) is a highly efficient uricosuric agent and is now used extensively. The dosage required to maintain the serum urate level at normal or near normal varies from 0.5 to 3.0 gm per day. In the majority of patients a daily dose of 1.5 gm is needed, but the optimum amount should be determined by serial blood level studies made at intervals of two to four weeks. Gutman and Yü[2] determined that about 10 per cent of patients need only 0.5 gm daily, 25 per cent require 1.5 to 2.0 gm daily, 50 per cent need 1.0 gm and only 15 per cent require more than 2.0 gm a day to maintain satisfactory blood urate levels. Such amounts are capable of increasing urate excretion by as much as 50 to 200 per cent, and prolonged administration usually leads to a softening, reduction in size and even disappearance of existing tophi.

The patient should drink sufficient water to insure a daily urinary output of 2,000 ml or more, since probenecid increases the chance of uric acid stones. Alkalinization of the urine is not recommended unless there is a history of urinary calculi. Salicylates counteract the action of probenecid and should not be used in conjunction with it.

Sulfinpyrazone (Anturane®), an analogue of phenylbutazone, is another highly efficient uric acid diuretic. The uricosuric action of sulfinpyrazone is well sustained over long periods of administration, and recommended dosage is from 200 to 400 mg a day, the uricosuric action of 400 mg a day being comparable to that of 1.5 to 2.0 gm or more of probenecid a day. Doses of 400 mg a day have been found to increase urate excretion by 30 to 60 per cent.[1,3] Side effects are few, and the drug may be used successfully as a substitute for probenecid in the long-term treatment of chronic gout. At times sulfinpyrazone may be the urate diuretic of choice, especially in patients who have gastrointestinal intolerance to probenecid or who experience increased frequency of acute attacks with its administration.

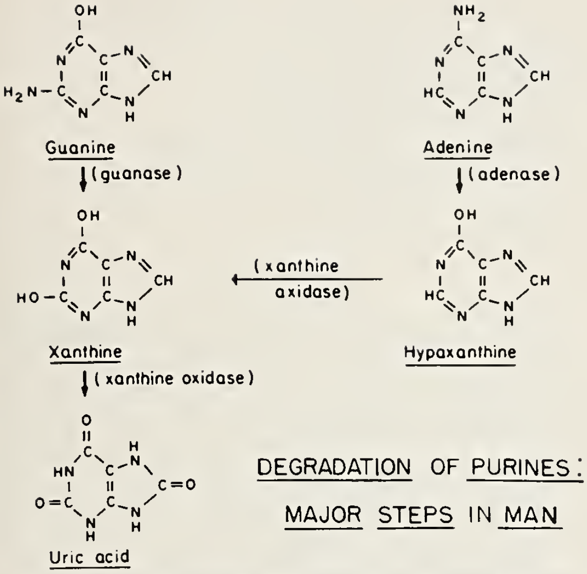


Chart 2.—Degradation of purines: major steps in man.

Allopurinol. An exciting and promising new approach to the treatment of gout has followed the discovery of allopurinol (Zyloprin®, HPP). A few years ago, during the course of investigations on the effect of thiopurines in patients with leukemia and lymphomas, it was found that allopurinol and several of its analogues reduced urate production and thereby lowered blood and urinary levels of uric acid. It followed logically to test the influence of the drug in patients with hereditary gout.

Allopurinol is actually an analogue of hypoxanthine. Its action is entirely different from that of probenecid; it lowers uric acid by interfering with the production of uric acid and does not act as a uric acid diuretic. Allopurinol is a xanthine-oxidase inhibitor. The major steps in the degradation of purines to uric acid are shown in Chart 2. The enzyme responsible for the conversion of the purines, hypoxanthine and xanthine to uric acid is xanthine-oxidase. Allopurinol inhibits the action of xanthine-oxidase, thereby reducing the conversion of purines to uric acid.

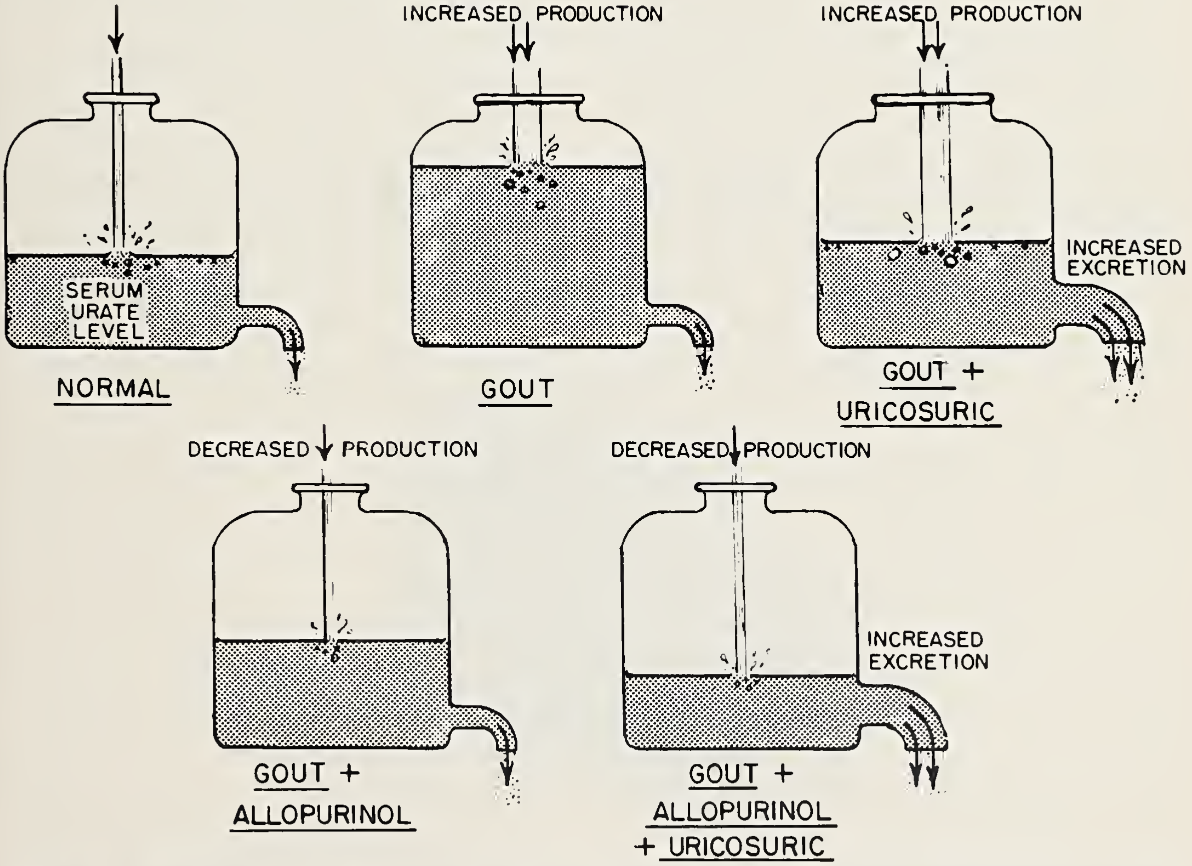


Chart 3.—Illustrating effect of allopurinol and uricosuric agents in control of both abnormalities of urate metabolism in gout—overproduction and underexcretion.

It decreases endogenous production whereas probenecid increases excretion. With its administration, uric acid levels in the blood and urine can be lowered to normal or below within a few days. They can be held there almost indefinitely, unless the disease is extraordinarily severe or kidney function is extremely impaired.

The results of large treatment series have now been reported, especially by Rundles and associates[5,6,8] at Duke University. In general, the response of patients with gout to allopurinol has been striking and the drug is tolerated very well. So far, no serious toxic effects have been encountered from allopurinol. An increased tempo of acute attacks may follow the rapid lowering of uric acid either by allopurinol or uricosuric drugs. This makes it worthwhile to start with low doses and to give colchicine concomitantly to suppress acute attacks during the early months of administration. Doses of 200 to 400 mg a day, given by mouth in divided doses, are usually sufficient to control cases of moderate disease. Rarely are doses greater than 600 mg a day required, even in the presence of urate nephropathy, which today serves as the most important indication for its use.

Allopurinol and uricosuric agents, such as probenecid or sulfinpyrazone, are effective when given together, actually complementing each other. So it now appears that at last we have arrived at a point where both abnormalities of urate metabolism in gout—namely, overproduction and underexcretion—can be therapeutically controlled (Chart 3).

Generic and Trade Names of Drugs

Phenylbutazone—*Butazolidin*
Indomethacin—*Indocin*
Adrenocorticotropic hormone—ACTH
Triamcinolone acetate—*Kenalog*
Methylprednisolone acetate—*Depo-Medrol*
Probenecid—*Benemid*
Sulfinpyrazone—*Anturane*
Allopurinol—*Zyloprin,* HPP

REFERENCES

1. Burns, J. J., Yü, T. F., Ritterbrand, A., Perel, J. M., Gutman, A. B., and Brodie, B. B.: A potent new uricosuric agent, the sulfoxide metabolite of the phenylbutazone analogue, G-25671, J. Pharm. and Exper. Therapeutics, 119:418, 1957.

2. Gutman, A. B., and Yü, T. F.: Protracted uricosuric therapy in tophaceous gout, Lancet, 2:1256, 1957.

3. Gutman, A. B.: The search for uricosuric agents suited to the management of tophacous gout, New York J. Med., 63:576, 1963.

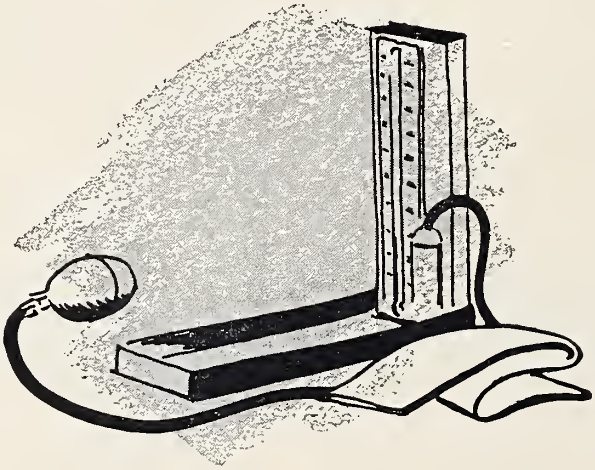
4. McCarty, D. J., and Hollander, J. L.: Identification of urate crystals in gouty synovial fluid, An. Intern. Med., 54:452, 1961.

5. Rundles, R. W., Wyngaarden, J. B., Hitchings, G. H., Elion, G. B., and Silberman, H. R.: Effect of xanthine oxidase inhibitor on thiopurine metabolism, hyperuricemia and gout, Trans. Assoc. Amer. Physicians, 76:126, 1963.

6. Rundles, R. W., Metz, E. N., and Silberman, H. R.: Allopurinol in the treatment of gout, Ann. Intern. Med., 64:229, 1966.

7. Seegmiller, J. E., Howell, R. R., and Malawista, S. E.: The inflammatory reaction to sodium urate, J.A.M.A., 180:469, 1962.

8. Wyngaarden, J. B.: Xanthine oxidase inhibitors in the management of gout, Arth. and Rheum., 8:883, 1965.



Pesticide-Induced Illness

Public Health Aspects of Diagnosis and Treatment

IRMA WEST, M.D., *Berkeley*

■ *Over the past 25 years there has been a remarkable proliferation of new chemicals into our environment, among them the 57,000 different trade-named pesticide formulations now for sale in the United States. With them have come many new problems to physicians needing up-to-the minute toxocologic information, and also sizable problems in public health. Technology must be harnessed to bring to physicians, when they need it, help in the diagnosis and treatment of poisoning and other adverse effects from modern chemicals, for at present it is impossible for the practicing physician to keep up with what is known and unknown about the toxicology of all of these chemicals.*

MAN HAS MANIPULATED his environment on so large a scale that he has inadvertently invented and produced a multitude of the most complicated new problems ever to confront the health professions. Unfortunately, we have been slow to realize that plans for health and safety should be built into technologic advances in the planning stages. By the time technical tools are in operation and their use results in undesirable and unexpected effects upon people and their environment, the best opportunity to minimize these effects efficiently and humanely is largely lost. So it is with many of our new environmental health problems whether they are air pollution or other environmental contamination with modern chemicals, including pesticides.

Pesticides are materials which mitigate or kill unwanted animal or plant life. About 650 have been invented in the last 25 years. These new chemicals, plus a few older ones, are formulated into over 57,000 trade name products registered for sale in the United States. Never before have hundreds of new chemicals possessing such varying degrees and kinds of potential for good and harm been introduced into the environment in so short a time.

It is important that problems in environmental medicine be viewed in context. With the possible exception of drugs, pesticides have been the first great experiment in the mass use of chemical technology. About one hundred million pounds of pesticides are now applied annually in California. Ten years ago about half that amount was applied and 20 years ago use of the new synthetic pesticides was just beginning. By far the greatest portion of pesticides is used in agriculture. Only 1 per cent is applied for control of disease vectors. About 59 per cent of the pesticides used are insecticides, 15 per cent fungicides, 15 per cent defoliants and herbicides, 10 per cent fumigants and 1 per cent rodenticides.

Presented before the Section on Environmental Health at the Annual Meeting of the California Medial Association, Los Angeles, 19 to 23 March 1966.

From the Bureau of Occupational Health, State of California Department of Public Health, Berkeley.

Reprint requests to: Bureau of Occupational Health, 2151 Berkeley Way, Berkeley 94704.

Pesticides have brought great benefits—and, with them, disturbing adverse side effects which are summarized in Table 1.

A question which naturally arises is, do the benefits outweigh the adverse side effects? The answer depends, of course, on what values one assigns to the items listed. The food technologist, the agriculturist and the chemical manufacturer will point to the sizable benefits as the more important—the food surpluses, the economic importance of the commodities where pesticides play a significant role in production or preservation. On the other hand, the biologist, the conservationist and the wildlife expert will look with alarm at the chain of events arising from the worldwide contamination of the environment with the persistent chlorinated hydrocarbon pesticides, including the insidious build-up of these chemicals in the food chains. Medicine and public health have interests in both sides of the picture. Worldwide, pesticides have been one of the methods used in successfully combating malaria and other vector-borne diseases. Millions of lives have been saved. In California the threat of Western and St. Louis Equine viral encephalitis is held in check by the mosquito abatement activities. On the other hand, deaths and serious illness from acute pesticide poisoning and other recognized adverse effects upon California citizens which occur regularly are a tragic and unnecessary waste of human health and life (See Tables 2 and 3). Further, the uncertainties about long-term effects upon people arising from a contaminated environment and from the storage of chlorinated hydrocarbon in human fat, are reason for considerable uneasiness in the medical profession and among public health workers. There is, of course, no objective answer to the question of the relative value of the benefits versus the adverse side effects from pesticides. Information on which to make such a judgment is far from complete and may never be available. However, as time goes on the relative importance of these benefits and side effects may become more obvious.

A question of greater significance from the standpoint of public health and environmental medicine is, can we have the benefits of pesticides without the undesirable side effects? It is technically feasible and well within the realm of possibility to use pesticides in a manner which will reduce undesirable side effects to almost zero. However, such a program would call for revolutionary changes in our standards for research and field testing, and in our control over developing technology. We can obtain as much protection against the adverse side effects as we are willing to insist upon and pay for.

The prevention of untoward effects upon the health of the population arising out of our technology is emerging as a most important and difficult public health function. Our society has never really faced the issue of what would be necessary to prevent the undesirable side effects arising from the use of pesticides and still enjoy their benefits. First, before a pesticide was put into general use, it would be necessary to know, through research and field tests, what all of the potential undesirable effects are. Second, these chemicals must really be controlled so that they will not be used in a manner producing adverse effects. Third, because methods for predicting adverse effects cannot be expected to be perfect, they must be continually evaluated and a monitoring system for human health must be established with built-in power to stop and revise uses of pesticides when they become suspect of producing undesirable effects.

This kind of system may seem insurmountably difficult, but that is because our administrative vision has never been big enough for our environmental health problems. A good control program is technically feasible. It has been routine, for

TABLE 1.—*Benefits and Undesirable Side Effects Arising from the Use of Pesticides*

Benefits	*Undesirable Side Effects*
Enhance production of food and fiber.	Human poisoning and other diseases from pesticides.
Help preserve stored food and other commodities.	Contamination of the environment with destruction of beneficial plant and animal life such as bees and wildlife; concentration of chlorinated hydrocarbons in food chains.
Help control vector-borne disease.	Pesticide residues on food.
Help control nuisance pests.	Storage of chlorinated hydrocarbon pesticides in human and animal fat.
Protect economically and aesthetically valuable resources (forests, parks, trees, lumber, flowers, gardens, etc.).	Development of resistance to chemicals by pests.

example, in the development of our space program. However, when it comes to down-to-earth matters involving the general population, too little too late is more often the case. Air pollution is another example of a situation in which our administrative imagination and machinery has never been big enough to catch up and come to grips with the problem.

Using hindsight in analyzing the genesis of undesirable and often unexpected side effects from pesticides, it is apparent that considerable research and control went into some aspects of pesticide usage and very little into others. A great deal of research and attention was paid to establishing tolerances for pesticides on crops in which pesticides were applied. Applications of pesticides were carefully prescribed and the crops monitored. Crops with more than the legal tolerances were condemned. However, pesticide poisoning among workers applying these materials and contamination of the environment, for example, received very little if any research attention or effective control. It is also apparent that the skills and technical knowledge employed in the development of pesticides were in fields related to the intended uses of pesticides. Technical skills related to the adverse side effects were often not included.

It should be stated at this point that there are very distinguished scientists who are not optimistic about our ability to control unwanted side effects arising from our technological tools. For example, Dr. Rene Dubos (15 April 1965 *Journal of Occupational Medicine*) is quoted as follows:

"Present programs for controlling potential threats to health from new substances and technologic innovations are doomed to failure because we lack the scientific knowledge to provide a sound basis for control.

"Current testing techniques have been developed almost exclusively for the study of acute, direct toxic effects.

"In contrast, most untoward effects of the technological environment are delayed and indirect. . . . Yet little is being done in schools of medicine and public health or in research institutes or government laboratories to develop the kind of knowledge that is needed for evaluating the long-range effects on man of modern ways of life.

"The dangers associated with ionizing radiation, or with cigarette smoking should have sensitized the public as well as scientists to the importance of delayed effects. But, surprisingly, this knowledge has not increased awareness of the fact that most other technological innovations also have delayed effects.

"The slow evolution of chronic bronchitis from air pollutants, the late ocular lesions following use of chloroquine, the accumulation of the tetracyclines in the fetus, and of course all the carcinogenic effects, are but a few of the countless objectionable results of new substances or technologies which appeared at first essentially safe."

The same scientist spoke to the same point in a statement appearing in *Bioscience*, 14:11, January 1964:

"There is no need to belabor the obvious truth that, while modern science has been highly productive of isolated fragments of knowledge, it has been far less successful in dealing with the complexity of natural phenomena, especially those involving life. In order to deal with problems of organized complexity, it is therefore essential to investigate situations in which several interrelated systems function in an integrated manner. Multifactorial investigations will naturally demand entirely new conceptual and experimental methods, very different from those involving only one variable, which have been the stock in trade of experimental science during the past 300 years and to which there is an increasing tendency to limit biological research."

The time has come to state that the medical profession has been placed in a difficult position with respect to the recognition and treatment of untoward effects upon human health from pesticides and other modern chemicals. Since the field is one of growing potential for liability, it is somewhat surprising that so little protest has been heard from physicians. The present mechanisms for bringing information and education to physicians are not geared to meet today's rapid introduction of hundreds of new chemicals of potentially dangerous effect. It is entirely unrealistic to expect every physician in general practice to keep up with what is known and unknown about the toxicologic properties of modern chemicals. Since technology produced this urgent problem, it is only fair to expect it should be used to devise imaginative new procedures to bring to the physician, when he needs it, effective help and up-to-date information to assist in the diagnosis and treatment of poisoning and other conditions re-

TABLE 2.—*Accidental Deaths Attributed to Poisoning from Pesticides and Other Agricultural Chemicals California 1951-1965**

		Number of Deaths										
		Children				Workers				Others		
Year	Total	Total	Arsenic	Organic Phosphates	Other	Total	Organic Phosphates	Methyl Bromide	Other	Total	Arsenic	Other
1951-65 Total	128	76	44	13	19	29	12	7	10	23	0	13
*1965	5	2	1	1	0	1	0	1	0	2	0	2
1964	2	1	1	0	0	1	1	0	0	0	0	0
1963	6	3	1	1	1	1	1	0	0	2	0	2
1962	5	4	1	2	1	1	1	0	0	0	0	0
1961	6	3	2	0	1	3	2	0	1	0	0	0
1960	4	4	4	0	0	0	0	0	0	0	0	0
1959	18	10	4	2	4	5	1	2	2	3	1	2
1958	13	6	2	0	4	3	1	1	1	4	3	1
1957	12	8	5	1	2	2	1	0	1	2	1	1
1956	18	11	9	1	1	4	0	2	2	3	2	1
1955	6	3	1	0	2	1	0	0	1	2	2	0
1954	12	9	3	4	2	2	1	0	1	1	1	0
1953	10	4	3	1	0	4	3	0	1	2	0	2
1952	6	5	4	0	1	1	0	1	0	0	0	0
1951	5	3	3	0	0	0	0	0	0	2	0	2

Source: State of California, Department of Agriculture, Annual Reports, Bureau of Chemistry, 1951-1960; State of California, Department of Public Health, Death Records and Occupational Disease Attributed to Agricultural Chemicals, 1951-1963 by Bureau of Occupational Health.

*All 1965 data preliminary, a small number of death certificates yet to be processed.

Note: Suicides now outnumber accidental deaths from pesticides (13 in 1964, 19 in 1965).

sulting from exposure to pesticides. Also urgently needed is the development of many more clinical chemical laboratory tests to help the physician confirm a diagnosis. For many chemicals, such tests either do not exist or are not available locally. Circumstantial and clinical evidence alone are often quite inadequate to arrive at a sound diagnosis. As a result there are probably more unsound diagnoses and more missed diagnoses in chemical poisoning than in most other areas of medicine.

One of the most immediate problems in public health is the lack of information about what effects pesticides and other modern chemicals are having in the population. Only a part of this information is available through death certificates, the Doctor's First Report of Work Injury (See Tables 2 and 3) and an occasional research project.

These problems of the practicing physician and public health suggest the possibility of a joint solution. A state or national center to provide

TABLE 3.—*Reports of Occupational Disease Attributed to Pesticides and Other Agricultural Chemicals for All Conditions and Systemic Poisoning, California 1953-1964*

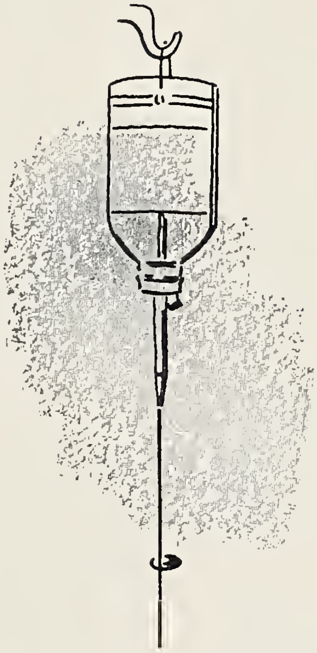
	Reports of Occupational Disease				
		Systemic Poisoning			
	Total	Total	Attributed to Organic Phosphates (Phosphate Esters)	Attributed to Chlorinated Hydrocarbons	Attributed to Other Agricultural Chemicals
Total	9,894	3,296	2,412	141	743
1964	1,328	230	135	24	71
1963	1,013	345	267	14	64
1962	827	219	140	21	58
1961	911	268	194	14	60
1960	975	368	283	7	78
1959	1,093	499	407	10	82
1958	910	328	227	14	87
1957	749	252	189	12	51
1956	789	281	197	11	73
1955	531	183	126	4*	53
1954	391	122	101	1*	20
1953	377	201	146	9*	46

*DDT only.

Source: State of California, Department of Industrial Relations, *Doctor's First Report of Work Injury.*

Statistics compiled by Bureau of Occupational Health, Department of Public Health.

medical and toxicological consultation to physicians with diagnostic and treatment problems could, at the same time, record, mechanize and analyze case data for study and dissemination. Any number of benefits to physicians, their patients and the public could arise from such a center. For example, unexpected effects upon health could be picked up and documented much earlier and appropriate preventive measures taken; the physician would have help in obtaining and interpreting laboratory tests; and liability problems would be minimized. This proposal is for an advanced stage in the development of the Poison Information Centers now in use. It is time we recognized the value of augmenting a valuable service of this kind to meet the needs of the day.



Pharmacology and Diagnosis of Pesticide-Induced Illnesses

RUTHERFORD T. JOHNSTONE, M.D., *Los Angeles*

■ *Although emphasis upon the concept of environmental health is a recent development in the medical community at large, the environment in which man worked has been of considerable concern to physicians in occupational medicine for a quarter of a century or more.*

Among the environmental factors which may adversely affect the health of exposed persons are the pesticides. The pharmacologic properties of these chemicals as well as the diagnostic signs and symptoms are presented herein.

ALTHOUGH this 95th annual convention of the California Medical Association is the first in which special attention is given to environmental health, the concern regarding at least one area of man's environment is not new.

About a quarter of a century ago in the very hotel in which the CMA meets today, a group of physicians met to plan the formation of the Western Association of Industrial Physicians. At that time and for some years afterward, industrial medicine was primarily concerned with the treatment of trauma. Twenty-five years ago concern over the environment within the walls of industry was just emerging. Today it is nice to recall that the aforementioned group took cognizance of this aspect of occupational medicine.

With the advent of the chemical age in the United States the American Medical Association realized that industrial medicine was no longer surgical in nature. Chemical hazards altered the environment. So the American Medical Association created its Council on Industrial Health, now the Council on Occupational Health. Soon this Council became burdened by problems, which were caused by industry but involved the community, such as air and water pollution, pesticide poisoning, radiation fallout and others. In 1959 the Council recommended the creation within the American Medical Association of a Committee on Environmental Health. More recently the California Medical Association, ever alert to the health care of our citizens, formed its own Committee on Environmental Health.

Some of us rejoice in this mutation in health care—that from a practice once low on medicine's totem pole, occupational medicine conceived and gave birth to a concept of concern regarding man's physical, chemical and biological environment. Today, almost always, the air within the mill, foundry or factory is healthier to breathe than the urban atmosphere. And, we might add that while 70 to 80 million workers and their families thrill to the drama of surgical operations on the brain or heart as depicted on TV, they are unaware of the silent, undramatic preventive medical program existing where they work.

Today's Prominent Pesticides

Grouped under the word *pesticide* are the insecticides, fumigants, fungicides, weedicides, rodenticides, repellants and attractants, to name a few. Before the advent of chlorophenothane

---

Presented as part of a Panel Discussion on the Diagnosis and Treatment of Pesticide Induced Illnesses at a Conference on Environmental Health at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 520 W. 7th Street, Los Angeles 90014.

(DDT), the war waged against pests utilized (and, most often, futilely) certain metalloid substances such as arsenic and a few botanical derivatives such as pyrethrum, rotenone and nicotine. Compounds containing arsenic and nicotine are still widely used in the home garden. Since their toxic effects are generally well known, they will not be discussed here. Of greater interest today are the synthetic chlorinated hydrocarbons and the organic phosphate esters.

The Chlorinated Hydrocarbons

At present there are approximately 700 pesticidal compounds of all classes. Obviously only a group consideration can be given as to toxic effects.

Pharmacology

The exact mechanism of action of these insecticides on man is unknown. Animal experimentation and clinical studies have indicated that these chemicals stimulate the cerebellum and the higher motor cortex. In severe intoxication, such stimulation causes clonic and tonic convulsions or epileptiform seizures.

Diagnosis

The diagnosis of pesticidal poisoning is rarely difficult in a person not in coma who gives a history of exposure. It should be readily suspected in a comatose adult who handles these chemicals in his work. In children who are violently ill or comatose, the ingestion of a poison of whatever nature should be suspected. If the child is found in the garden or garage, a pesticide should be strongly suspected, be it a chlorinated hydrocarbon, a phosphate ester or the vehicle for such chemicals.

Signs and Symptoms

The primary effect of the chlorinated hydrocarbon insecticide is narcosis. The synthetic chlorinated hydrocarbons are capable of an additional effect—hyperexcitability of the central nervous system. This is thought to be due to variations in the arrangement of the molecular structure of these chemicals.

If the exposure is mild, there may be a feeling of fullness of the head, with dizziness or drowsiness. Sometimes this is accompanied by nausea and vomiting. Increased exposure results in headache and lethargy and, in more severe cases, stupor or coma. Coma may be accompanied by choreic or athetotic movements or convulsive seizures. The symptoms consist of narcosis plus hyperexcitation of the central nervous system. Ingestion of these insecticides produces the same signs and symptoms but the onset is often more rapid and the gastrointestinal symptoms more violent.

In the differential diagnosis, the pertinent factors are an absence of fever, blood cell counts and blood chemical contents within normal range and an absence of change in blood pressure unless the victim is having seizures. A reliable diagnostic aid is electroencephalographic evidence of diffuse cortical discharges, assuming that the electroencephalogram was normal before the suspected poisoning.

Laboratory Findings

Except for evidence of the insecticide or its derivatives in the stomach contents, the urine or fat tissue, laboratory findings are largely nonspecific. More recently, analytical procedures are being made available to detect a number of the members of this group of compounds and their metabolites.

Mention is made of the electroencephalogram because a few of the chlorinated hydrocarbon insecticides are known to cause an epileptiform seizure.

Phosphate Ester Insecticides

Commonly designated as the organic phosphates (erroneously as the "nerve gases") the phosphate ester group of insecticides was introduced about 1947. Prominent among these organic phosphates are the pyrophosphates, the thiophosphates and the phosphonates or phosphoamides.

Probably the first organic phosphate to be introduced in the United States for use as an insecticide was tetraethylpyrophosphate (TEPP). Almost simultaneously, recognition was extended to parathion, a nitrophenyl phosphorothionate. Because of its more ready acceptance as an insecticide, the toxic effects of parathion on man have been subjected to intensive study. As a result, the toxicity of parathion represents a denominator to which most other organic phosphate insecticides are compared.

Pharmacology

An appreciation of the pharmacologic actions of the phosphate esters is basic to diagnosis, to prognosis, to appropriate treatment and to the estimation of disability. The point of action is the enzyme cholinesterase. As a result of the inhibition of this enzyme, acetylcholine accumulates in the tissues. This causes stimulation of the "cholinergic" portions of the autonomic nervous system and stimulation and paralysis of the central nervous system and the neuromuscular apparatus. In man the erythrocytes contain a specific cholinesterase enzyme and the plasma contains a nonspecific one. Measurement of red cell cholinesterase has shown that depression of enzyme activity to symptomatic levels (about 30 per cent of normal) may occur rapidly as a result of a single dose of a potent inhibitor or gradually over a period of days or weeks as a result of frequent small exposures. During the reverse phase or recovery from inhibition, sufficient cholinesterase activity usually returns within 24 to 48 hours to permit adequate functional recovery, but it may take weeks or months for enzyme activity to return to normal levels.

Diagnosis

After undue exposure, the onset of symptoms may be delayed for from a few minutes to several hours. Usually the victim first notices headache, nausea and generalized weakness. These symptoms are followed by giddiness, abdominal cramps, blurred vision, profuse sweating, salivation and constriction of the chest with difficulty in breathing. Severely intoxicated persons have uncontrollable muscle spasms, convulsions and coma. Convulsions and coma do not necessarily indicate an unfavorable outcome if proper treatment is started immediately and continued vigorously.

Attention should be called to one sign that has been emphasized in the literature to the point of confusion. Miosis is a frequent presenting sign. However, it may not appear until quite late, and therapy should not be delayed merely because miosis is not noted initially. In fact, miosis may be preceded for a time by mydriasis.

Differential Diagnosis

Because of the wide range of signs and symptoms produced by phosphate ester intoxication, unrelated entities demand consideration. Among agricultural workers exposed to excessive heat, heat stroke or heat exhaustion is not uncommon. Other conditions to be considered are hypoglycemia, brain hemorrhage and severe respiratory infections. Asthmatic attacks also may simulate mild phosphate ester poisoning.

The patient's reaction to atropine is useful in the differential diagnosis. If he complains of dryness of the mouth after being treated with even small doses of atropine, he does not have phosphate ester poisoning. (Protopam chloride is supplanting the use of atropine for this test.)

Comment

Experience indicates that in cases of intoxication from the phosphate ester group recovery is almost always complete once the cholinesterase activity is restored. Indeed, functional recovery may ocur before the cholinesterase returns to the patient's normal baseline.

In contrast to the phosphate esters, we are less certain about the residual effects of repeated or prolonged exposure to the synthetic chlorinated hydrocarbon pesticides. Occasionally it is alleged that members of this group have caused transient liver or kidney damage. To date my experience with cases in which the intoxication resulted from inhalation or percutaneous absorption does not support that contention. I have had no experience with fatal or near-fatal cases due to ingestion.

Of more interest is the question of whether there exists a relationship between exposure to the synthetic chlorinated hydrocarbon pesticides and blood dyscrasias, especially aplastic anemia. In this regard the finger of suspicion has been pointed to the gamma isomer of benzene hexachloride (lindane). At present the question is controversial.

Few other chemicals have aroused so much interest among the medical profession, the press and the public as have the pesticides. As with the furor over fluoridation, the use of pesticides has induced fanatical denunciation in a few areas of interest. In the range of statements by those who oppose the use of pesticides, one may find assertions that almost any of the synthetic chlorinated hydrocarbon pesticides may cause almost any kind of blood dyscrasia, but such sweeping contentions find no support among authorities in the field of toxicology. An analysis of the case histories from which such assertions emanated reveals that an assumption of relationship was made upon the basis that the patient at some time was exposed to a pesticide. However, the assumption becomes invalid when it becomes apparent that the patient did not have signs or symptoms of pesticide intoxication.

HISTOPLASMOSIS

A Review of Three Cases Studied in San Diego County

V. J. WYBORNEY, M.D. AND HENRY WALCH, PH.D., *San Diego,*
ALAN B. LOEFFLER, M.D., *Escondido,* and ROBERT M. WHITA, M.D.,
Jasper, Alabama

■ *Three cases of histoplasmosis, a disease seldom reported in California, were diagnosed clinically by the authors in San Diego County. It is probable that there is a higher incidence of this disease in California than is at present recognized.*

Travel history, histoplasmin skin testing and serologic studies for mycotic infection are important in the diagnosis. Cultures of secretions and biopsy material are of great value if positive; but negative cultures (at least in non-endemic areas) do not rule out the disease. Travel and migration to and from endemic areas present opportunities for this disease to constitute a diagnostic problem far from the geographic area in which the disease was acquired.

Although usually benign, histoplasmosis may be severe in the acute state, may disseminate or may be chronically active and progressive. Amphotericin B is the only effective chemotherapeutic agent and it is usually reserved for these forms of the disease.

MANY EXCELLENT PAPERS thoroughly cover histoplasmosis in endemic areas.* Loosli,[20] estimated that 30 million people in the United States are infected with histoplasmosis capsulatum. Fungal infections now rank fourth in the United States as cause of death from infectious diseases.[16] Histoplasmosis is known to occur in California and it is possible the incidence is much higher than is recognized. A high index of suspicion is important in atypical cases since histoplasmosis may simulate more common diseases. In the present age of swift travel and constant migration, histoplasmosis must always be considered by physicians anywhere in the United States and particularly in California in light of the great influx of new people. We can no longer consider the Mississippi River Basin as "the endemic area." Surveys in "non-endemic areas" show positive skin reactions in as many as 70 per cent of persons tested.[5] Yet, review of CALIFORNIA MEDICINE and of *California and Western Medicine* for the period 1936-1965 revealed only two reports dealing with three cases of active histoplasmosis. Diagnosis was by lung biopsy in one case, one by x-ray films of the chest, skin tests, serologic studies and residence history, and one by autopsy.

Reports of Cases

Following are reports of three additional cases discovered in San Diego County. Each is different from the others roentgenologically and clinically.

Submitted 20 April 1966.

Reprint requests to: 2291 Fifth Avenue, San Diego 92101 (Dr. Wyborney).

*Reference Nos. 1, 8, 14, 31, 35, 36.

CASE 1.—A nine-year-old white girl had dry cough, malaise and slight fever in June 1962. She had lived on the west coast all her life but in May 1962 visited Kansas City, Missouri. While there she spent several hours in an abandoned chicken coop playing with newborn puppies. Results of hematologic studies were within normal limits except for the blood sedimentation rate which was 42 mm in one hour. An x-ray film of the chest showed a widened mediastinum and multiple 1 cm radiopaque soft-bordered nodules scattered in both lung fields (Figure 1). Histoplasmin skin tests were weakly positive. Tests with purified protein derivative No. 2 and coccidioidin 1:100 were negative. A scalene node biopsy also was negative. Histoplasmosis complement fixation was positive (1:256).

After two months' bed rest followed by limited activity for several months, partial clearing was noted and the sedimentation rate decreased. In August 1963 low grade fever and malaise again developed and there was an increase in the scattered nodular infiltrates and persistence of the widened upper mediastinum. Several weeks of bedrest again was followed by improvement as observed by serial x-ray films, resumption of normal temperature and decrease in the sedimentation rate. In September 1964, after an interval improvement, new infiltrates were again noted roentgenographically. After three months' bedrest roentgen studies still showed progression of disease. These findings were accompanied by fever, malaise, dry cough and blood sedimentation rate ranging between 40 and 50 mm in one hour.

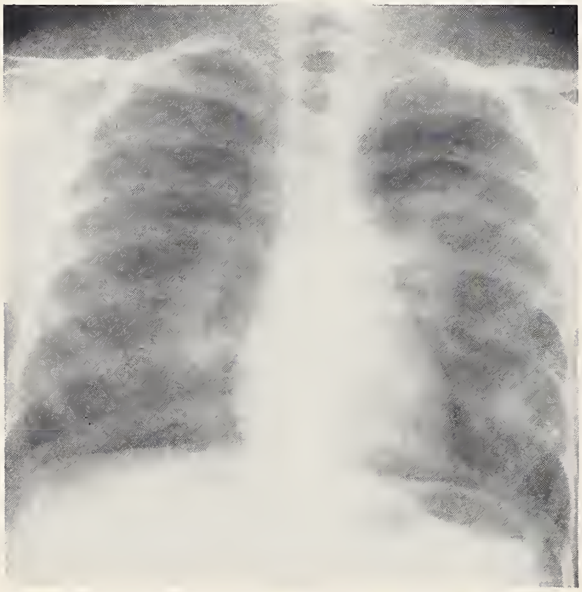


Figure 1.—(Case 1) Multiple nodular infiltrates are scattered in both lung fields. There is rather pronounced widening of the upper mediastinum attributed to enlargement of the hilar and mediastinal lymph nodes.

Treatment with amphotericin B was begun in January 1965 at a dose of 1 mg per kg of body weight. By late March 1965, the patient had received a total of approximately 0.8 gm (more than 25 mg per kg of body weight). Serial x-ray films showed distinct partial clearing of the nodular pulmonary infiltrates and some decrease in the extent of mediastinal involvement. The symptoms completely abated during treatment with amphotericin B and the sedimentation rate decreased from 42 mm to 22 mm. A slight elevation of the blood urea nitrogen occurred and hemoglobin decreased 20 per cent.

During the summer of 1966 low grade temperature elevation and malaise again occurred, persisting several weeks. In September the temperature decreased to normal range, the patient was feeling well but histoplasmosis complement fixation was still positive at 1:128. It appeared that further chemotherapy might be required.

CASE 2.—An eight-year-old white boy had onset of symptoms in September 1959. Although born in San Diego, the patient had visited Kentucky in June 1959. While there, he helped gather eggs in a chicken house. A skin test with histoplasmin 1:100 was strongly positive in October 1959. Radiographs of the chest (Figure 2) showed infil-

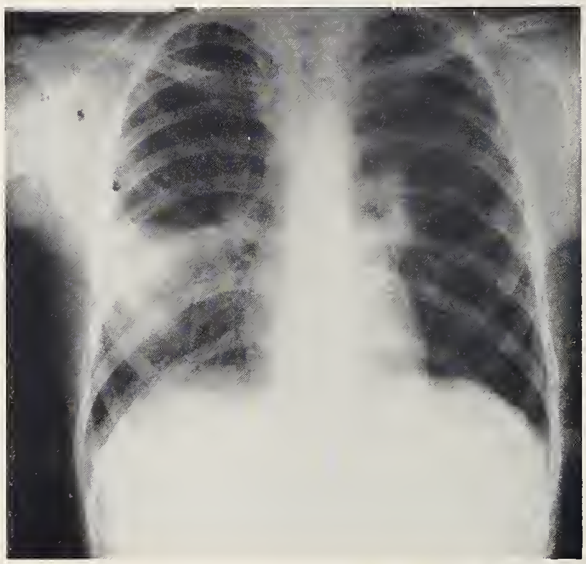


Figure 2.—(Case 2) The right hilar structures are enlarged as are the left hilar structures to a lesser degree. Dense clouding throughout the region of the right middle lobe.

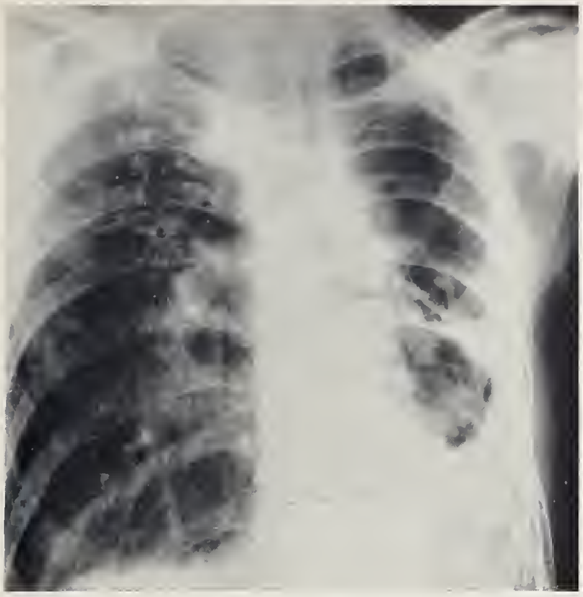


Figure 3.—(Case 3) A large aircontaining structure presumably a cavity, occupies about two-thirds of the left lung field. A smaller cavity approximately 4 cm in diameter is situated in the right upper lung field. Numerous fine infiltrates throughout the remainder of the lung.

tration and/or atelectasis of the right middle lobe with bilateral hilar adenopathy. Tests with PPD No. 2 and coccidioidin 1:100 were negative. Histoplasmin skin test (1:100) was positive. Complement fixation was positive (1:256 titer) for histoplasmosis and negative for coccidioidomycosis.

At last report (May 1963) the patient appeared to have had prompt and complete recovery with no treatment other than bed rest in the fall of 1959. This case is an example of benign pulmonary histoplasmosis.

Case 3.—A 57-year-old white man who had lived in Illinois and Missouri until 1950 complained of cough, loss of weight, weakness and expectoration. The cough began in 1941 and in 1958 he became unable to work. He had not been east of the Rockies since 1950. Radiographs of the chest (Figure 3) showed extensive infiltration in both lungs, the left lung largely destroyed by cavitary disease. Except for a positive reaction to histoplasmin, all skin tests were negative. Multiple sputum cultures in several laboratories were negative for tubercle bacilli and fungi. Mouse inoculation of sputum by one of the authors at San Diego State College identified the pathogen as histoplasma capsulatum. These findings were confirmed by culture at the Kansas City field station of the U.S.P.H.S. and by complement fixation titer of 1:512. Serologic titers for coccidioidomycosis were negative.

Studies of this patient at San Diego County Hospital 1960 to 1963 showed the disease still active. Complement fixation titer was 1:256. Sputum cultures again were negative. (The patient has since died in a custodial hospital.) This case indicates that eight years away from an endemic area does not preclude the presence of serious histoplasmosis. There was no history of corticosteroid therapy, and no evidence of debilitating underlying disease (such as lymphoma) which might activate histoplasmosis was noted during four years of observation.

Extrapulmonary dissemination apparently did not occur in any of these three cases.

Clinical Features

Conrad and coworkers[8] described histoplasmosis as a disease of protean manifestations. Case 1 is an example of non-cavitary, chronically active, progressive pulmonary histoplasmosis with considerable involvement of mediastinal lymph nodes. Case 2 is an example of benign pulmonary histoplasmosis with mediastinal lymph node involvement spontaneously clearing. Case 3 is an example of the chronic progressive cavitary-type which, untreated, frequently results in death.[12,18,19]

The most common form of histoplasmosis, no doubt, is the more completely benign form with no clinical or subjective manifestations, resulting in a positive histoplasmin skin test and frequently in pulmonary calcifications.[31] The disseminated form has the poorest prognosis and most frequently attacks young[6,9] and debilitated elderly persons. The early recognition of dissemination is imperative so that therapy can be begun. Pulmonary histoplasmosis may present as an apparently inactive form of the disease. Some patients, however, show very slow progression by roentgen examination and complement fixation titers.[35] Histoplasmosis is the most frequent cause of benign pulmonary granuloma.[9] It is not surprising that 10 per cent of the patients in tuberculosis sanitoria have unrecognized histoplasmosis,[31] either alone or existing with tuberculosis, since the chronic active progressive form is roentgenographically indistinguishable from cavitary tuberculosis. Twenty per cent of this group with unrecognized disease have negative histoplasmin skin tests and 10 per cent have negative serologic tests. Recognition is imperative since this form of disease is progressive and, without treatment, fatal.[31] The less common manifestations of histoplasmosis are Addison's disease,[9] endocarditis,[27] pericarditis,[17] mediastinitis and superior vena caval obstruction.[33] Perhaps many of the "idiopathic" diseases of the heart and the fibrosing lesions of the mediastinum and retroperitoneum are in reality manifestations of histoplasmosis. Likewise, sarcoidosis is simply a non-caseating granulomatous reaction which in appearance is exactly like the non-caseating granulomatous reaction of histoplasmosis. Finally, bronchiectasis is a very common sequela of histoplasmosis.[36]

Incubation Period

In various epidemics reported (that is, in so-called endemic areas) the incubation period varies from four to 21 days.[13,24,28] It would appear that this varies according to the host reaction. In Case 2 reported herein, four months elapsed between brief exposure (1 June 1959) in an endemic area and the first symptoms (September 1959).

Diagnosis

Diagnosis may be laborious and baffling. Culture either on artificial media or by mouse inoculation is the surest method, and it is far from certain; even in active cases only 50 to 60 per cent of multiple cultures are positive. Since highly skilled, experienced microbiologists are a prime requisite, this diagnostic approach is frustratingly unreliable in non-endemic areas. Yeast bodies can alter the organisms morphologically and they may be encapsulated for years.[36] At certain phases the organisms cannot be grown by present methods. When the organism is grown from contaminated material, the media must have streptomycin and penicillin added. Once these antibiotics were thought to inhibit pyogenic contaminants, but now it is known that these substances enhance the growth.[6] Obviously, therefore, the use of either streptomycin or penicillin in vivo is contraindicated. Sputum cultures are worthless unless a lung lesion has a bronchial extension.

Skin testing is an important aid in diagnosis. The purport of the reaction is like that of the reaction to tuberculin in patients with tuberculosis, but anergy occurs more frequently than in tuberculosis, particularly in histoplasmosis of disseminated type.[6] In short, skin reaction is useful epidemiologically but a negative test does not preclude the disease. Negative skin tests for tuberculosis and coccidioidomycosis are also helpful in the differential diagnosis of histoplasmosis. However, since even in severe coccidioidal infection the skin test may be negative, serologic studies for coccidioidomycosis should also be done, as they were (with negative results) in the three cases herein reported. Serum for complement fixation should be drawn before or at the time of the skin test, because skin testing done before the specimen is drawn can bring about positive complement fixation in an inactive case or increase the titer in a proven case.[22]

Serologic testing is the touchstone for diagnosis of histoplasmosis in cases of lung disease of doubtful cause. Serologic findings must be correlated with clinical history, history of travel, skin tests and roentgen findings. It is useless to do histoplasmin skin testing in diagnostic problems unless serologic studies are also done if the reaction is positive. In spite of disagreement among authorities as to what constitutes a positive complement fixation tests, a titer of less than 1:8 seems of little diagnostic significance and higher than 1:64 always significant.[12,30] Serologic tests are usually positive during active disease and remain positive for a variable duration up to a year or more. A high rising titer is a good indication of active disease.[1] On the other hand, negative tests are not unusual in the presence of active disease.

The problem is further complicated, particularly for California physicians, since serologic cross reactions occur with coccidioidomycosis and blastomycosis. In fact, the authors of a report on one large series of young adults state that "all or most of the histoplasmin sensitivity found in California, Arizona and New Mexico probably represents cross sensitization by infection with coccidioides immitis.[21] Even though California is an endemic area for coccidioidomycosis, the patient's geographic history is important (although of decreasing value because of the widespread dissemination of the histoplasmosis capsulatum organism). In the past, coccidioidomycosis titers of 1:32 or greater were considered to signify possible dissemination, and the higher the titer the worse the prognosis. However we have observed several cases in which titers were higher than 1:32 and the patients recovered without dissemination. It is in the mild cases of coccidioidomycosis, where the complement fixation tests may be low or undetectable, that differential diagnosis becomes a test of acumen although not actually a problem, since the patients are not ill. In addition, in proven cases of histoplasmosis with a titer of 1:160 or more, the reaction to coccidioidin is never greater than 1:20.[4] Recent studies of the fluorescent antibody inhibition test for histoplasmosis may improve the serologic diagnosis. At any rate the standardization of the test will be improved.[15]

There is no definite characteristic roentgenographic appearance associated with histoplasmosis. Roentgen studies contribute most when serial radiographs are correlated with the clinical course and laboratory studies.

Epidemiology

The mode of infection is by inhalation of the fungus from exogenous sources in nature. Apparently it is high organic content of bird excreta which promotes growth of the fungus in soil, and birds do not necessarily have or carry the active disease.[13] The fowl family, even the common starling, has been indicted as a carrier of this organism in the excreta.[25] At any rate, histoplasmosis has been cultured from soil at random.[10] This is not surprising, since histoplasmosis is the most common fungous disease of the animal kingdom.[38] Even so, epedemiologic surprises still occur—to wit, the report of a case in Great Britain in a person who had never been out of the country and had nothing to do with soil, animals or fowl. Only 14 other cases have been reported in England and surprisingly five of these were of the acute disseminated form.[23] On the other hand, among the natives of Panama the incidence of positive skin reaction to histoplasmin is high but the disease is rarely manifested clinically.[34] Very often the source of infection in infants is unknown, since they are not likely to have had contact with soil, particularly those who have not left the hospital since birth. In one case, feathers in a pillow were proved to be the source of infection in an infant.[11]

Treatment

Treatment of this disease is reviewed in many articles[2,29,32,37] as well as textbooks of pharmacology. Amphotericin B given intravenously appears to be the only effective antifungal agent currently available commercially. A total dosage of 25 mg per kg of body weight given over a period of several weeks is usually required when treatment is necessary. The toxicity of amphotericin B is such that it is indicated principally in severe acute infections, in chronic active disease and in the disseminated forms of histoplasmosis.

REFERENCES

1. Baum, G. L., and Schwarz, J: Pulmonary histoplasmosis, New Engl. J. Med., 258:676-684, 3 April 1958.

2. Beatty, O. A., Leven, N., Saliba, A., and Coelbo, J.: Surgical therapy of chronic pulmonary histoplasmosis with and without Amphotericin B, J. Thoracic and Cardiovascular Surgery, 44:228-237, August 1962.

3. Bryner, S., and Kaufman, S. F.: Pulmonary histoplasmosis—A report of two cases, Calif. Med., 86:47-50, January 1957.

4. Campbell, C. C., and Binkley, G. E.: Serologic diagnosis with respect to histoplasmosis, coccidioidomycosis, and blastomycosis and the problem of cross reaction, J. Lab. and Clin. Med., 42:896-906, December 1953.

5. Chase, H. V., and Campbell, C. G.: Histoplasmin skin test, survey of elementary school children in Frederick County, Md., J.A.M.A., 183:335-338, October 1962.

6. Christie, Amos: The disease spectrum of human histoplasmosis, Ann. Int. Med., 49:544-555, September 1958.

7. C.P.C.: Presentation of case, Calif. Med., 65:29-31, July 1946.

8. Conrad, F. G., Saslaw, S., and Atwell, R. J.: The protean manifestations of histoplasmosis as illustrated in 23 cases, Arch. Int. Med., 104:692-709, November 1959.

9. Editorials: Histoplasmosis, J.A.M.A., 173:914, June 1960.

10. Emmons, C. W.: Isolation of histoplasma capsulatum from soil, Pub. Health Rep., 64:892, 1949.

11. Evans, H. E., Campbell, C. C., and Utz, J. P.: Infantile disseminated histoplasmosis, A case reporting pillow feathers as a source of infection, J.A.M.A., 181: 999-1000, September 1962.

12. Furcolow, M. L., Dato, I. L., Tash, F. E., Lynch, H. J., Jr., Follison, R. F., Atwell, R. I., Veatly, O. A., Brashear, C. A., Yates, J. L., Dickey, A. B., Petrikas, A., Pierce, G. N., Rogers, H. C., Smiley, G. W., and Wilmore, R. C.: Course and prognosis of untreated histoplasmosis, A United States Public Health Service Cooperative Study, J.A.M.A., 177:292-296, August 1961.

13. Grayston, J., Thomas, J. D., and Furcolow, M. L.: The occurrence of histoplasmosis in epidemics—Epidemiological studies, Am. J. Public Health, 43:665-676, June 1953.

14. Horton, G. E., Larkin, J. C., and Phillips, S.: Acute pulmonary histoplasmosis, So. Med. J., 52:912-919, August 1959.

15. Kaufman, L., Schubert, J. H., and Kaplan, W. D.: Fluorescent antibody inhibition test for histoplasmosis, J. Lab. and Clin. Med., 59:1033-1038, June 1962.

16. Kinney, T. D.: Basic contributions to medicine by research in pathology, J.A.M.A., 179:264, 1962.

17. Klieger, H. L., and Fisher, E. R.: Fibrocalcific constrictive pericarditis due to histoplasma capsulatum, New Engl. J. Med., 267:593-596, September 1962.

18. Lehan, P. H., Brasher, C. A., Larsh, H. W., and Furcolow, M. L.: Evaluation of clinical aids to the diagnosis of chronic progressive cavitary histoplasmosis, Am. Rev. Tuberc., 75:938-948, June 1960.

19. Loewen, D. F., Procknow, J. J., and Loosli, C. G.: Chronic active pulmonary histoplasmosis with cavitation, A clinical and laboratory study of 13 cases, Am. J. Med., 28:252-280, February 1960.

20. Loosli, C. G.: Histoplasmosis. Some clinical, epidemiological and laboratory aspects, M. Clin. North America, 39-171, 1955.

21. Manos, N. E., Ferebee, S. H., and Kerschbaum, W. F.: Geographic variation in the prevalence of histoplasmin sensitivity, Dis. of Chest, 29:649-668, June 1956.

22. McDearman, S. C., and Young, J. M.: The development of positive serologic tests with histoplasma capsulatum antigens following single histoplasmin skin tests, Trans. 19th Conf. on Chemother. Tuberc., VA-Armed Forces, 1960, p. 310.

23. Miller, A. A., Ramsden, F., and Geake, M. R.: Acute disseminated histoplasmosis of pulmonary origin probably contracted in Britain, Thorax, 16:388-394, December 1961.

24. Minor, G. R., and Corey, J. H., Jr.: An epidemic of histoplasmosis in a family, Dis. of Chest, 35:409-414, April 1959.

25. Murdock, W. T., Travis, R. E., and Sutliff, W. D.: Acute pulmonary histoplasmosis after exposure to soil contaminated by starling excreta, J.A.M.A., 179:73-75, January 1962.

26. Okudaira, M., Straub, M., and Schwarz, J.: The histologic features of the histoplasmin skin test in dogs, Am. J. Path., 40:721-727, June 1962.

27. Palmer, R., Geraci, J. E., and Thomas, B. J.: Histoplasma endocarditis, Arch. Int. Med., 110:131-137, September 1962.

28. Perkins, R. L., Saslaw, S., and Ockner, S. A.: Migration histoplasmosis, Ann. Int. Med., 57:363-371, September 1962.

29. Procknow, J. J.: Effectiveness of X-5079C in the treatment of disseminated histoplasmosis and blastomycosis, J. Lab. and Clin. Med., 60:1005-1006, December 1962.

30. Richert, J. H., and Campbell, C. C.: The significance of skin and serologic tests in the diagnosis of pulmonary residuals of histoplasmosis, A review of 123 cases, Am. Rev. Resp. Dis., 86:381-384, September 1962.

31. Rubin, H., Furcolow, M. L., Yates, J. L., and Brasher, C. A.: The course of prognosis of histoplasmosis, Am. J. Med., 27:278-288, August 1959.

32. Saliba, A., Beatty, O. A., and Pacini, L.: Pulmonary histoplasmosis associated with pulmonary tuberculosis, So. Med. J., 55:249-256, March 1962.

33. Salyer, J. M., Harrison, H. N., Winn, D., Jr., and Taylor, R. R.: Chronic fibrous mediastinitis and superior venacaval obstruction due to histoplasmosis, Dis. of Chest, 35:364-377, 1959.

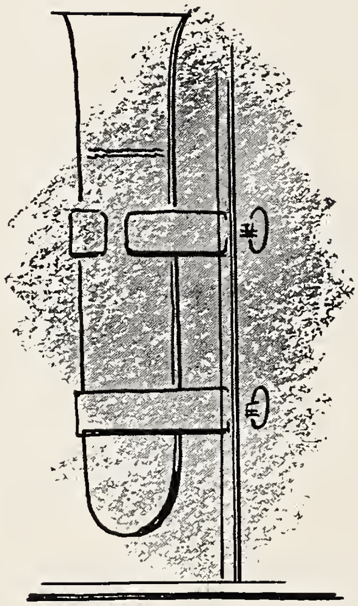
34. Shirokov, E. P.: Histoplasmosis in Panama. Despite high incidence of positive histoplasmin skin reactors among natives and long-term residents, clinical manifestations of the diseases are practically never seen, J.A.M.A., 177:297-299, August 1961.

35. Sweany, H. C., Gorelick, D., Coller, F. C., and Jones, J. L.: Pathologic and some diagnostic features of histoplasmosis in patients entering a Missouri hospital, Dis. of Chest, 42:1-15, July 1962.

36. Sweany, H. C., Gorelick, D., Coller, F. C., and Jones, J. L.: Pathologic and some diagnostic features of histoplasmosis in patients entering a Missouri hospital, Dis. of Chest, 42:281-305, September 1962.

37. Yates, J. L., Atay, M. N., Langeluttig, H. V., Brasher, C. A., and Furcolow, M. L.: Experience with amphotericin in the therapy of histoplasmosis, Dis. of Chest, 37:144-156, February 1960.

38. Zinsser's Textbook of Bacteriology—Tenth Edition. Appleton-Century-Crofts, Inc., New York, 1952, pp. 897-901.



Oxyphenbutazone (Tandearil®) In Rhinoplasty

A Clinical Evaluation of Effectiveness

BYRON J. BAILEY, M.D. AND ALAN M. NAHUM, M.D., *Los Angeles*

■ *To evaluate the effectiveness of Oxyphenbutazone as an anti-inflammatory agent, a double-blind study of Oxyphenbutazone and a placebo in a group of 42 patients who had nasal cosmetic operations involving osteotomy was carried out. The observations included direct objective measurement of the width of the palpebral fissure after operation, grading of the severity of postoperative edema and ecchymosis from photographs, and observations by the patients regarding the clearing of the postoperative discoloration. It appeared from the results of these observations that Oxyphenbutazone is not effective in preventing postoperative edema in such operations or in promoting more rapid resolution of postoperative edema. It did appear to enhance the clearing of postoperative periorbital ecchymosis.*

FOLLOWING TRAUMA to tissues an inflammatory response occurs that is characterized by pain, swelling, warmth and discoloration. Microscopically, one may observe migration of fluid and cells to the area of injury. This may be followed by formation of a fibrin clot filled with cells. Later, devitalized tissues and cells are ingested and removed from the area of injury and the reparative process commences simultaneously. Capillary proliferation and fibroblasts initiate the healing process. This reaction to injury is generally accepted as being of value in the process of tissue repair. However, certain aspects of the response are subjectively uncomfortable and in plastic surgical procedures about the face they may interfere with a cosmetic result.

The use of anti-inflammatory agents is based upon the hypothesis that they may be effective in the inhibition of some of the facets of the inflammatory response which adversely affect the final result, which in cosmetic surgery is the final appearance of the wound or the area of surgical trauma. This hypothesis has been tested by scores of investigators in a variety of situations, with widely varying conclusions. After reviewing this subject, one is left with the impression that many important aspects of the response to trauma are not well understood and that it is not known which of these phenomena is responsible for occasional final unfavorable cosmetic results.[9,10]

Types of Drugs Available

Several groups of pharmacologic agents are utilized in an attempt to limit the inflammatory response. These include salicylic acid and derivatives; glucocorticoids (cortisone, cortisol, synthetic steroids, etc.); and phenyl pyrazolone and

---

From the UCLA Center for the Health Sciences, Department of Surgery (Head and Neck), Los Angeles, and Division of Otolaryngology, Harbor General Hospital, Torrance.

Presented before the Section on Otolaryngology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Division of Otolaryngology, Harbor General Hospital, 1000 W. Carson Street, Torrance 90509 (Dr. Bailey).

derivatives (aminopyrine, dipyrone, phenyl butazone); and enzymes.

Anti-Inflammatory Steroids

The major class of drugs that have been employed for anti-inflammatory effects is the steroids, but use of them has been limited because of several major undesirable effects such as sodium retention, potassium excretion, alteration of carbohydrate metabolism and gastrointestinal ulceration. The mere effect of antagonizing certain aspects of wound healing and decreasing resistance to skin infection would seem good reasons for not using the drugs in association with accidental or surgical trauma. It is possible that chemical manipulation of the corticoid molecule will lead to compounds with decreased undesirable effects.[6,11]

Enzymes

Several enzymes have been proposed and are currently available for use as anti-inflammatory agents.[1,2,3,12] It has been claimed that these enzymes are capable of fibrinolysis or dissolution of fibrinous deposits that occlude small blood and lymphatic vessels, and thus of reducing inflammation, edema and collections of blood.

The following preparations are currently available:

Preparation	*Administration*
Streptokinase-streptodornase	Intramuscular, topical, oral
Chymotrypsin	Oral, topical
Bromelains (Ananase®)	Oral
Alpha amylase	Oral, topical
Proteolytic enzymes from papaya	Oral
Trypsin	Oral, topical

The use of these enzymes is based both upon a specific pathological response to trauma and a proposed mechanism of drug action. However, there is not sufficient evidence to prove that fibrin plays a significant harmful role in the production of edema and inflammation. In addition, there is no evidence that, *in vivo,* these drugs act as they are supposed to. Further, it is possible that they may interfere with a part of the normal healing response to surgical trauma. No studies are available to show that these drugs are circulated in their chemically active state long enough to be effective. On the other hand, there are several compounds in the body which inactivate these enzymes.[15]

One article[14] described the use of alpha-chymotrypsin in a dose of 10,000 Armour units injected intramuscularly immediately upon completion of surgical operation and then 5,000 units twice daily for the next four days. The operation was considered successful in 72 per cent of a controlled trial in 300 cases of plastic surgical procedures in the facial area.

Oxyphenbutazone

The non-steroid anti-inflammatory agents may be the most promising drugs to date. Oxyphenbutazone, one of the newest, may be of particular interest. While the drug has attracted particular interest in the treatment of collagen diseases, certain studies have been performed with regard to plastic operations.

The largest series[8] reported was 360 patients, half of whom were controls. The drug was given for five days, commencing the day before operation. In most of the treated patients, a definite decrease in pain, swelling and redness was observed. The first day 600 mg was given in three divided doses, then daily for the next four days 400 mg in four divided doses.

Other studies[4,5,13] have also indicated that the drug decreases postoperative pain and inflammation and that there were no adverse effects either as to wound infections or the healing process. In addition, toxic side effects appeared to be virtually absent when the drug is administered for short periods.

Other Non-Steroidal Agents

Several non-steroid drugs possess significant anti-inflammatory actions. Some idea of the potency of some of these drugs as compared with cortisol acetate may be obtained from one study[6] in which the effects of administration to animals was observed. The study provided the following comparative values: With the effectiveness of cortisol acetate taken as 100, the effectiveness of chlorpheniramine maleate was in a range of 28 to 55; of dipyrone, 3 to 8; of phenylbutazone, 2 to 16; of amino pyrine, 2 to 14; of antipyrine, 1 to 5; and of cinchopen, 2 to 18.

An excellent summary and comprehensive review of recent work in this area by many investigators is presented in the collected papers of the International Symposium on Non-Steroidal Anti-Inflammatory drugs which was held in Milan in 1964.[7]

Clinical Study of Oxyphenbutazone

A clinical study was carried out to determine the effectiveness of oxyphenbutazone (Tandearil®) in preventing post-rhinoplasty inflammation and ecchymosis and in promoting the postoperative resolution of inflammation and ecchymosis.

Previous studies of this type have been criticized for lack of objectivity. One great difficulty even in a controlled study is that the variation in individual responses to trauma in general (and the trauma of cosmetic operations in particular) is so wide that one can only speculate about the amount of reaction that would have occurred if an anti-inflammatory agent had (or had not) been given. The present study was designed to evaluate oxyphenbutazone as objectively as possible in these circumstances.

The group studied was made up of 50 consecutive patients who were to have cosmetic operations on the nose.

During the course of analyzing the data, it was decided that eight patients must be removed from the study for the sake of statistical accuracy and clinical significance. Six of the eight were removed from the final analysis because osteotomy was not a part of the operation and they therefore had much less edema and ecchymosis. One patient was excluded because she did not take the drug the day before operation, and one patient was removed because she vomited the tablet the morning of operation.

Pertinent characteristics of the remaining study group of 42 patients are shown in Table 1.

A double-blind technique was utilized in the administration of the drug and a placebo which was inert and identical in appearance. The drug code was held by the UCLA Hospital Pharmacy and was not broken until after all of the final observations and evaluations had been recorded. The drug was given orally as follows: 600 mg the day before operation; 600 mg preoperatively on the day of operation; 200 mg a day on the first, second and third postoperative days. The operations were performed by three different residents, 31 by one of them, six by another and five by the third.

TABLE 1.—*Characteristics of Series of 42 Patients who had Rhinoplastic Operations*

	Treated with			
	Tandearil®	*Placebo*	*Total*	*Per Cent of Total*
Total in study	21	21	42	100.0
SEX				
Male	6	8	14	33.3
Female	15	13	28	66.7
AGE				
10 to 19	3	1	4	9.5
20 to 29	12	10	22	52.4
30 to 39	5	4	9	21.4
40 to 49	1	5	6	14.3
50 to 59	0	1	1	2.4
PREVIOUS NASAL OPERATIONS	0	3	3	7.1
PREVIOUS FRACTURE	7	6	13	31.0

Direct objective caliper measurements were made of the maximum amount the patients were able to open their eyes. This technique, not previously described, is an accurate and objective method of evaluating post-rhinoplasty edema. The measurements were made on the first and fifth postoperative days (frequently by more than one observer) to evaluate both the initial decrease in palpebral fissure width and the rate of return toward normal.

In addition, the patients were graded on the severity of the inflammatory response and the periorbital ecchymosis. This was recorded on the basis of a graded scale designed as follows: Grade one, minimal detectable inflammation and ecchymosis; Grade two, mild; Grade three, moderate; Grade four, pronounced inflammation and ecchymosis (inability to open one or both eyes). This grading was done on the first and fifth postoperative days by the same observer (or group of observers). At the conclusion of the study the same kind of grading was done from color photographs by two investigators, working separately. The photographs, taken on the first and fifth postoperative days, made it possible to review the entire series of patients at one time, thus minimizing variations in grading criteria by the observer.

Since it was not possible to see all patients daily after they left the hospital, each was instructed very carefully to make note of the date on which periorbital discoloration was no longer apparent. This date was quite significant for most patients, since they were reluctant to return to school or to work until it had been reached. It is also an observation that deserves particular attention because it is one of great practical importance in determining the justification for use of an anti-inflammatory agent. While the ultimate cosmetic advantage of modifying the inflammatory response remains a subject for academic controversy, if a patient can be returned to school or work two or three days earlier (and without the risk of serious side effects) then the expense of the drug is justified.

As to toxicity, we were concerned primarily about the possibility of bone marrow suppression, rash, gastrointestinal irritation and possible increase in operative bleeding (which has been attributed to some anti-inflammatory agents). Careful notation was made of any symptoms referable to any of those conditions. Leukocyte counts were performed preoperatively and on the tenth postoperative day.

Results

Measurement of the Palpebral Fissures

On the first day after operation there was no statistically significant difference in the measurements between those who received Tandearil® and those receiving the placebo, hence no objective evidence that Tandearil® prevented postoperative facial edema.

From the first postoperative day to the fifth, there was no statistically significant difference in the measurements between the Tandearil® group and the placebo group and, therefore, no objective evidence that Tandearil® enhances the normal resolution of postoperative edema.

Severity of Edema and Ecchymosis

Grading of the degree of edema and ecchymosis by observers during the patient's stay in hospital (Table 2) gave no statistical evidence that Tandearil® prevented postoperative edema and ecchymosis or that it enhanced the resolution toward normal. The same was true of grading the severity of the postoperative edema and ecchymosis from color photographs at the completion of the clinical phase of the project.

TABLE 2.—*Estimate of Facial Edema by Physician on Clinical Observation (Double-blind Graded in Range of 1 to 4)*

	Patients Treated with			
	Tandearil®		*Placebo*	
	Number	*Per Cent*	*Number*	*Per Cent*
GRADE OF EDEMA DAY 1 POST-OP				
1	4	19.0	1	4.8
2	12	57.1	10	47.6
3	4	19.0	9	42.9
4	1	4.8	1	4.8
DAY 5 POST-OP				
1	6	28.6	4	19.0
2	11	52.4	8	38.1
3	4	19.0	7	33.3
4	0	0.0	2	9.5
CHANGE IN GRADE BETWEEN DAY 1 AND DAY 5				
Decreased:				
1.5 grades or more	1	4.8	1	4.8
1.0 grades	3	14.3	4	19.0
0.5 grades	4	19.0	0	0.0
No change	8	38.1	11	52.4
Increased:				
0.5 grades	1	4.8	3	14.3
1.0 grades	2	9.5	2	9.5
1.5 grades	1	4.8	0	0.0
2.0 grades	1	4.8	0	0.0

Patients' Observations

The patients' statements as to the day the discoloration had cleared were tabulated (Table 3). Approximately half of them had noted clearing by the eighth postoperative day and half required longer. For this reason, eight days was taken as an arbitrary dividing line for the group, and it then was noted that 71.4 per cent of the patients who had received Tandearil® had noted clearing by the eighth day, whereas 71.3 per cent of those who received the placebo required more than eight days for the ecchymosis to resolve.

The average time for clearing of the discoloration was eight days for the Tandearil® group and ten days for the placebo group. This finding is statistically significant ($p<0.05$) and supports a conclusion that Tandearil® appears to enhance the clearing of postoperative ecchymosis.

Toxicity

Leukocytes in the Blood

The mean values for the leukocyte counts (Table 4) rose in both the Tandearil® and the placebo groups. There was no statistically significant difference between the groups.

Gastrointestinal Intolerance

The only observations in this regard occurred in two patients who vomited shortly after receiving

TABLE 3.—*Patients' Observations of Number of Days Required for Disappearance of Facial Bruising*

	Treated with			
	Tandearil®		*Placebo*	
Days	*Number*	*Per Cent*	*Number*	*Per Cent*
5	0	0.0	1	4.8
6	2	9.5	0	0.0
7	5	23.8	0	0.0
8	8	38.1	5	23.8
Total within 8 days	15	71.4	6	28.6
9	3	14.3	4	19.0
10	0	0.0	2	9.5
11	2	9.5	4	19.0
12	1	4.8	3	14.3
13	0	0.0	2	9.5
Total longer than 8 days	6	28.6	15	71.3

TABLE 4.—*Mean Leukocyte Counts*

	Pre-op	*Post-op*	*Difference*
Tandearil® (20 pts)	8,897	9,591	+694
Placebo (16 pts)	8,236	8,817	+581

*The greatest leukocyte count decrease was 3,550 and it occurred in a patient who received the placebo.

the tablets the morning of operation. One received Tandearil,® the other the placebo.

Hemorrhage

No excessive bleeding was noted at the time of operation or afterward in either group.

Effect on Healing

No evidence of delayed healing was observed during the course of this study in the patients who received Tandearil.® It is obviously more difficult to evaluate the "rate of healing" in operations of this type, as there is no visible incision to observe.

Generic and Trade Names of Drugs

Oxyphenbutazone—*Tandearil.*
Bromelains—*Ananase.*

REFERENCES

1. A.M.A. Council on Drugs: Enzymes proposed as systemic anti-inflammatory agents, J.A.M.A., 188:875, 8 June 1964.

2. Avakian, A.: Current concepts in therapy: Chymotrypsin and trypsin, New Engl. J. Med., 264:764, 1961.

3. Bogner, R. L., and Snyder, C. C.: High dosage oral chymotrypsin as an adjunct in plastic surgery, Int. Coll. Surg. J., 37:289, 1962.

4. Connell, J. F., and Rousselot, L. M.: The clinical evaluation of a new anti-inflammatory agent, Am. J. Surg., 98:31, 1959.

5. Connell, J. F., Jr., Wallace, R., and Rousselot, L. M.: A clinical evaluation of oxyphenbutazone in surgical inflammatory lesions, Am. J. Surg., 101:435, 1961.

6. Dorfman, R. I., and Dorfman, A. S.: Anti-inflammatory activity of non-steroidal agents in a rat granuloma assay, Proc. Soc. Exp. Biol. and Med., 119:859, 1965.

7. Excerpta Medica International Congress Series: Internat. symp. on non-steroidal anti-inflammatory drugs, No. 82, Milan, 1964.

8. Hipps, C. J., Pasha, N. I., Lawson, J. M., and Straith, R. E.: Tandearil®: Its use in plastic surgery, J. Michigan State Med. Soc., 62:563, 1963.

9. Houck, J. C.: Chemistry of inflammation, Ann. N.Y. Acad. Sci., 105:765-812, 1963.

10. Laguna, J., and Guaman-Garcia: Metabolic effects of anti-inflammatory agents, pp. 264-277 in international symposium on injury, inflammation and immunity, Williams and Wilkins, Baltimore, 1964.

11. Lernar, L. J., Bianchi, A., Turkheimer, A. R., Singer, F. M., and Borman, A.: Anti-inflammatory steroids: Potency, duration, and modification of activities, Ann. N.Y. Acad. Sci., 116:1071-1077, 1964.

12. Miller, J. A.: Treatment of oedema by enzyme therapy, J. Canad. Dent. Assoc., 31:443, 1965.

13. Mitler, J. M., Ginsberg, M., Aree, S. Q., Bogosian, A., and Smith, L. B.: Clinical experience with oxyphenbutazone in the treatment of inflammation and edema, Antibiotic Med. and Clin. Ther., 7:109, 1960.

14. Moore, F. T.: Some further views on alpha-chymotrypsin in facial surgery, Brit. J. Plastic Surg., 16:387-390, 1963.

15. Shery, S., and Fletcher, A. P.: Proteolytic enzymes—a therapeutic evaluation, Clin. Pharm. and Ther.,1:202, 1960.

The Psychosomatic Emergency

CHARLES WILLIAM WAHL, M.D., *Los Angeles*

■ *Many psychiatric problems present themselves under the guise of physical rather than mental symptoms.*

These occur in several categories: (1) Psychological problems which work in conjunction with definitive organic pathology, such as the fear of death. (2) Symptoms produced by altered physiology or biochemistry resultant from an acute orchronic stress state. (3) A combination of A and B above. (4) Patients with an intense disease, such as hypochondriasis. (5) Psychiatric symptoms, such as depression, anxiety or apathy which develop antecedent or subsequent to a fearfully anticipated illness or procedure.

These patients have certain characteristics in common. (1) They manifest a disproportionate concern over symptoms. (2) The symptoms are inconsistent with the usual pattern of organic disease. (3) The onset is concurrent with states of conflict. (4) There is usually a personal and family history of psychic and psychosomatic disorders. (5) Other psychiatric disorders are usually present. (6) Secondary gain is usually evident.

These patients can be successfully treated within the hospital setting and within the framework of psychiatric consultation and psychotherapy.

THERE IS a whole category of psychiatric emergencies which are not, at least on first view do not seem to be psychological in character. The presenting symptoms are usually physical rather than "mental," and the patient's psychiatric difficulties are occult rather than overt. Not only are the symptoms those of physical illness, but the patient himself, is usually convinced that he is physically ill. In such cases the physician, too, impelled by the whole course of his training to first consider the organic causes which may produce the symptoms, may not at once recognize the basically psychiatric character of the patient's complaints. Such symptoms may closely simulate those of an organic illness or complicate an organic illness which may already be present. These are among the clinician's most taxing and challenging problems.

There are a variety of reasons why physical symptoms may be employed as a coverup for psychiatric difficulties. The first and most obvious is that it is still, to many persons, debasing and humiliating to have emotional problems but quite acceptable to have a physical illness. Often this cultural bias is reinforced by the attitude of the physician who may share that prejudice. Second, physical illness evokes a wide variety of helping responses. If a degree of incapacity warrants admittance to hospital, this may be equated by the patient with the receipt of loving care, the fulfill-

---

Associate Professor and Chief, Division of Psychosomatic Medicine, Department of Psychiatry, UCLA School of Medicine; Consultant in Psychiatry, Sepulveda Veterans' Administration, Camarillo State Hospital, and Metropolitan State Hospital; Member, Southern California Psychoanalytic Institute, Los Angeles, California.

Submitted 17 May 1966.

Reprint requests to: Department of Psychiatry, UCLA Medical Center, Los Angeles 90024.

ment of dependency longings or an honorable retreat from life's problems and responsibilities which pride might not otherwise afford.

The contrast of these conditions with those of a primarily psychiatric illness is most striking. Not only does the psychiatric patient usually feel ashamed of being ill, he often finds that he is an object of dread and aversion to others. If treatment in a psychiatric hospital is necessitated, this is equated with being "put away"—a far cry from the situation of a comfortable bed in a medical hospital where he can be solaced by visitors, surrounded by gifts of candy and flowers and deluged with get-well cards.

In addition to these situational and cultural disadvantages, there are also unconscious intrapsychic reasons which impel the patient to focus upon the physical aspects of his symptoms. The words *hurt, ache* and *pain* do double duty in our language. They may refer to strictly physical or strictly psychic states. Since the pains of the body are easier to endure than those of the mind, an unconscious substitution can take place. If the mechanisms of repression, denial, displacement and reaction-formation are excessively used as a way of avoiding psychical conflict and emotion, "body-language" is employed instead. The mind always chooses what it regards as the lesser of two evils. Physical suffering may be unconsciously viewed as preferable to psychic suffering and may also act as a guilty expiation of the latter. However, the relationships between mind and body are subtle and complicated. A patient cannot be expected to be aware of the physiological and biochemical disturbances that accompany or presage mental turmoil. The bent of his entire education, as indeed is also the physician's, reinforces the concept that physical pain or alteration of function is produced only by structural abnormality and is wholly physical in character. All of these factors combine to facilitate a focusing of attention and concern on physical rather than psychic distress. Hence, the most frequent initial manifestation of a psychiatric problem will usually be a complaint of physical symptoms; and the most frequent general hospital. It is here, consequently, rather than in a psychiatric facility, that such patients are first seen and their disease most easily diagnosed and treated.

Illnesses in these patients occur in several categories:

- In one category are patients who have unquestioned organic disease but who have concomitant psychic stresses which alter or complicate its management. An example is the patient with an overmastering fear of death or disability in relation to the primary disease. Other examples are instances in which the symptoms or complaint are manifestly disproportionate to the exciting organic cause.
- The largest group is made up of patients who have physiologic or biochemical changes produced by acute or chronic psychic stress. Examples are the usual psychosomatic illnesses and specifically those states of alteration of function which closely mimic organic diseases for example, psychogenic muscular dystonia, hyperventilation syndrome, cardiospasm, pylorospasm, aerophagia, psychogenic hypoglycemia, splenic flexure syndrome and tension cephalalgia and status medicamentosus.
- In a third group are patients with concomitant organic or psycho physiological illnesses in multiple combination.
- Another category is made up of patients with intense convictions of disease or those who have psychogenic interference with motor function without biochemical or physiological alteration, as in the conversion hysterias.
- A fifth category comprises psychiatric conditions such as depression, anxiety or apathy produced in consequence of the experience or anticipation of an illness or a therapeutic procedure. Examples are panic antecedent or subsequent to a surgical or obstetrical procedure, and intensified fear of disability or death.

These common categories by no means exhaust the possibilities.

All these patients have, however, certain characteristics in common which are helpful in diagnosis:

- Usually there is disproportionate concern regarding the symptoms (with the exception of the bland indifference of the conversion hysteric).
- The symptoms range widely in character and are not consistent with the usual pattern of organic disease syndromes.
- The onset of symptoms is concurrent with states of conflict and stress which the patient is unable to acknowledge or handle.
- There is usually a personal and family history of psychic and psychosomatic disorders.
- Other concomitant psychiatric disorders are usually encountered.

- There may be evidence of secondary gain or advantage accruing to the patient as a result of his illness.

It is generally considered that the treatment of patients whose psychiatric difficulties are expressed through the means of physical symptoms is one of singular difficulty. Somatic expression of psychic difficulties is presumed to be indicative of massive repression which prevents honest consideration by the patient of his underlying problems.

In my experience, the converse is the case. These patients are particularly accessible to psychiatric help and intervention, and one of the major reasons for this accessibility is the direct consequence of the hospital admission.

As physicians, we are habituated to hospitals. They are places in which we learn, treat and work, and they have, therefore, a variety of pleasant and reassuring connotations. To the patient who does not share this background, the hospital is often an alien world and to be put into a hospital is an anxiety-producing experience. Except for imprisonment, no other circumstance in our society requires one to surrender more of his personal liberty, prerogatives and identification.

Consider his state. In hospital, the patient is restricted by convention and necessity to a white rectangle, three feet by six feet, and is often required to maintain a special set of postures for long periods. Most of the time, he is isolated from persons of his own choosing or is exposed to other sick patients who have problems, suffering and idiosyncrasies of their own. Whatever his extramural fame or worth, he cannot show his individuality or status by dress but, like everyone else, must wear a routine hospital gown and take a bed number. The hours, methods and character of his awakening, eating and sleeping are specifically regulated. The privacy of the body and the bowel habits which are among the most personal of functions have to be greatly modified from his usual patterns. He also finds himself with a huge amount of time on his hands with very limited means of filling it. Access to his doctor and nurse is usually much less than he would wish. In addition to the natural worries about himself attendant upon any illness and the financial and other concerns resultant from it, he is often exposed to the sights of suffering and death which may have been quite foreign to his usual experience.

In short, the hospital experience can be and usually is to some degree, frightening; and this fear is compounded if the physical symptoms for which the patient is admitted are, in fact, emotionally based. It is well for us to remember that the "sick role" is often no bowl of cherries, magnifying as it does, the loss of major identity of oneself as a working, healthy, self-sufficient and self-directed person.

Paradoxical as it sounds, however, these implicit conditions serve to operate as decided advantages in the psychiatric consultation, and it is not difficult to see why this would be. The patient in a hospital often feels helpless in an alien and frightening environment. His full and individual self may be depersonalized to an identification as "that case of gallbladder in room 227." The regression and the heightened dependency upon others which inevitably accompany illness are intensified in a patient of this kind, yet he finds that the physician and the nurses cannot satisfy his increased need for time, explanations and reassurance. Hence the psychiatrist, who is not only specifically trained in the techniques of communication but is also prepared to spend the time required to get to know him fully and well, is usually extremely welcome.

With such patients there develops, in a fraction of the time that would otherwise be required, a state of strongly positive transference. This occurs since states of physical illness, acting in concert with the previously mentioned special conditions which characterize a stay in hospital, induce and intensify the kind and quality of regression that is achieved by the organically well patient only after many hours of outpatient psychotherapy. It is an axiom of psychoanalytic theory that access to the deepest repressions and to the conflictful material that patients defend against can only be effected in the posture of a strongly positive transference and with the development of that state of regression which will recapitulate and make more easily accessible early childhood repressed memories. The experience of being put in hospital and the organic illness can intensify and reinforce the physician-patient relationship, and as a result, deeply repressed and highly relevant material becomes quickly accessible and utilizable by the patient.

The fortunate consequence is that with such patients it is often possible to achieve striking psychotherapeutic results, not only toward alleviation of the presenting symptoms, but in the modification of the underlying character structure as well. With no other group of patients is this so fully possible.

In fact, this occurs so regularly that it is with just such categories of patients that the techniques of short-term, intensive, insight psychotherapy were developed by Deutsch, Jelliffe and others, and it is with such patients that these techniques are primarily taught and demonstrated to residents in psychiatric training.

The method of psychiatric consultation, and the psychotherapeutic work which follows it, proceed somewhat as follows:

At the outset, provision is made for privacy. The patient cannot be expected to speak candidly and openly of things that trouble him if he can be overheard. If necessary, the patient's bed should be moved to an unoccupied room. Then, after the therapist has introduced himself to the patient and has explained the purposes of the interview, the patient is encouraged to describe in detail the nature, course and progression of the symptoms. Careful attention is paid not only to the order or lack of it with which the history is related, but specific note is made of the "key words," these being the reiterated or idiosyncratic expressions or words which appear with unusual frequency in the stream of the patient's discourse. These are interrogatively repeated to the patient in a subtle manner by the examiner in order to evoke further associational material. Since they indicate emotionally laden conflicts, they produce in association material concerned with memories, events and personages which often have a significant relationship to the genesis and progression of the symptoms.

Careful note is also made during the interview of occult signs of anxiety and the coincident appearance of these with the events and personages being discussed. The most reliable of these signs prove generally to be the subtle twitchings of the muscles of the face, particularly the periorbicular and infraocular muscle groups and the twitching of the toes. Particular note is alto taken of the disparity between the consciously evinced anxiety and the signs of unconscious anxiety as shown by an elevated pulse rate, heightened skin temperature, hyperhidrosis and increased muscle tension.

Often the psychosomatically ill patient has all of the physiological signs of anxiety without being aware of the conscious emotion or effect which usually accompanies them. A helpful test is to note the response to anxiety-induced questions when interspersed with questions that are more benign. In highly anxious patients, the contrast in reaction between the two is greater than in other patients. The patient is also asked to describe the personalities of the significant figures of his past and present life. Careful attention is paid to the content and the affect of his responses as well as to the scope and character of these descriptions. The covertly anveious patient will be, usually, unable to describe or accept, mixed, conflictful or ambivalent feelings regarding significant persons of the present or past.

As the interview progresses, several characteristic things are discovered. The symptoms of the illness in a psychiatric disorder may be found to have appeared coincident with some conflictful event or circumstance in the patient's life. In addition, the symptoms usually manifest what has been called the autoplastic effect, which is to say that the patient's individual conception of his illness bears little relationship to medical facts but rather shown evidence of a highly personal distortion relevant from his own life history. Even educated persons will often display a number of bizarre and magical ideas concerning the functioning of the body parts which are related to the painful symptoms. In addition, there is also usually evidence that the illness or symptoms subserve some unconscious paleological, unwitting purpose to the patient. For example, the illness may operate as an assuagement of guilt, a suffering to guarantee immortality, a fulfillment of premonitory feelings of nemesis; or the illness may demonstrate anniversary reactions which are the development of a set of symptoms similar or identical to those experienced by some ambivalently regarded person in the past at the same chronological period. And last, there is usually evidence of a concomitant secondary gain. The symptoms enable the patient, often, to achieve some gratification which would not otherwise be able to be available to him or enable him to "fail with honor." From all of this data, the history and the communication of the patient as well as his relationship to the physician, the meaning and significance of the symptoms can be investigated and understood.

Because of the rapidity with which a close working relationship with the therapist develops in the hospital setting, it is possible to work psychotherapeutically with the patient with a much greater rapidity than would otherwise be the case. As in psychotherapy with other psychiatric patients, confrontation of the aspects of the ego defenses and the secondary gains of the symptoms are done first. With patients who manifest these symptoms, these confrontations can usually be made within the second hour of psychotherapeutic work. Interpretations of the unconscious meaning, value significance and utilization of the symptoms can usually be made by the third or fourth hour. In addition, explanations (educational interpretations) are freely given, both of the psychological and physiological facts as they apply to the patient's illness.

The meaning and utilization of the illness is early explored with these patients. It is often found that patients have a very distorted view of their anatomic and physiologic make-up, particularly in the area of their presenting symptoms. The reasons for this are vigorously explored, and the patient's latent repressed curiosity about the body and its functions gratified. The ways in which a physiologic or biochemical disturbances are productive of symptoms are also carefully explained. These explanations may also be reinforced by explanations as to the generality or universality of conflicts or circumstances which the patient may have felt to be a feature only of his own experience.

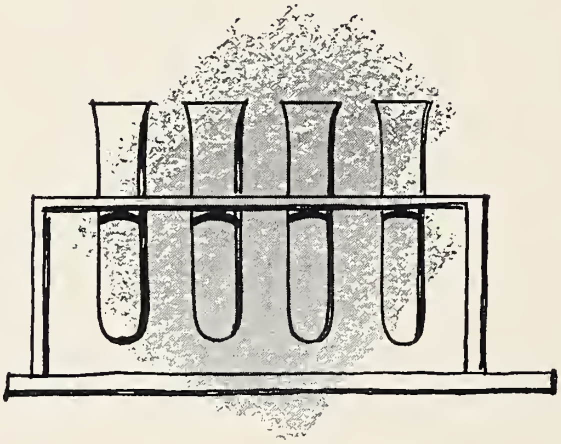
It is, initially, quite surprising as well as gratifying to discover how quickly patients can improve under so simple a regimen. It is usually possible to achieve gratifying and lasting psychotherapeutic results with a much lesser expenditure of professional time than one would ordinarily expect, and a speedy alleviation of symptoms in a kind of emergency, namely, the psychosomatic emergency, which often can be one of the most taxing, perplexing and refractory types of patient problem.

REFERENCES

1. Schottstaedt, William W.: Reaction to illness, Psychophysiologic Approach In Medical Practice, pp. 161-179, The Year Book Publishers, Inc., Chicago, Illinois, 1960.

2. Wahl, C. W.: Factors which affect symptom choice in psychosomatic medicine, New Dimensions In Psychosomatic Medicine (Edited by C. W. Wahl), pp. 27-43, Little Brown and Company, Boston, Massachusetts, 1964.

3. Weiss, Edward and English, O. Spurgeon: Psychosomatic Medicine, 2nd Ed., pp. 60-68, W. B. Saunders Company, Philadelphia and London.



CASE REPORTS

Clinically Severe Lactic Acidosis with Coma

JOHN R. PAYNE, M.D., *Woodland*

Lactic acidosis of severe degree with coma is usually fatal. In about 95 per cent of reported cases reviewed by Tranquada[4] in which therapy could be interpreted, the patient died. Careful documentation and evaluation of all clinical, metabolic and therapeutic data of such cases is therefore vital to further understanding and more rational therapy.

Elevations of lactate can vary substantially in degree. However, in clinically severe cases excess lactate levels often are between 10 and 40 mM per liter. Increased concentrations can be found after muscle exercise or secondary to many clinical situations in which substantial general tissue anoxia exists. In these instances excess production is probably the primary factor. Altered metabolism in liver disease or decreased utilization secondary to drug alterations of normal or usual metabolic pathways can result in lactate excess. Often, probably the initial factor or factors, such as drug effect or altered liver function, lead to accumulation that can result in diverse direct and compensatory changes resulting in, among other manifestations, hypotension, anoxia and further increases of lactic acid, thereby in a matter of hours forming a vicious and often fatal cycle.

The present case represented a state of severe clinical acidosis with associated derangement of blood chemical features in which a vigorous therapeutic program seemingly resulted in the successful outcome.

Report of a Case

A 52-year-old housewife was referred to the Woodland Memorial Hospital from an adjoining community on 22 November 1965. She had not been seen at this hospital previously. The patient had had known glycosuria dating back approximately 12 to 15 years and had been under supervision and active therapy for diabetes for five and a half years. At first, insulin had been given intramuscularly for control of diabetes, then oral medication for a year beginning approximately three years before admission, then reversion to 80 units of lente insulin a day about ten months before the present admission. The insulin dosage then was gradually lowered and after three months was discontinued. For seven months before admission the patient had been taking phenformin, (DBI), 25 mg four times a day.

The patient had cholecystectomy nine years before admission and she had been in hospital numerous times in the preceding four or five years for control of diabetes. Recently she had had no major disturbances to indicate clinical hypoglycemia nor was there a history of antecedent episodes of coma, of hepatic disease or, on careful questioning of friends and relatives, of alcohol intake.

Medications in addition to phenformin included hydrochlorothiazide (HydroDIURIL®) with potassium, taken once or twice a day and reserpine (Serpasil®) 2 mg three times a day. Antivert (meclizine dihydrochloride and nicotinic acid) one tablet once or twice a day had been used occasionally for dizziness but had not been used for sev-

---

From the Department of Internal Medicine, Woodland Clinic Medical Group, Woodland.

Submitted 10 March 1966.

Reprint requests to: Woodland Clinic Medical Group, 650 Third Street, Woodland 95695.

eral weeks preceding admission. Trihexyphenidyl (Artane®) 2 mg four times a day, was used to control a mild tremor; and, in the past, meprobamate had been taken occasionally.

The patient had had hypertension of moderate degree for many years. During the 18 months before admission, particularly during the months she was taking phenformin, she had progressively lowered her weight from 250 to 198 pounds. Symptoms of diabetic neuropathy had been present for some months, and a bilateral coarse tremor described as of the paralysis agitans type had been fairly well controlled with Artane.® She took care of a family of three and was able to do the full general work of the home.

Thirty hours before admission the patient had had sudden onset of pain which she described as originating in both sides of the neck and going down into the chest with pressure-like precordial discomfort. The day preceding admission she had moderate shortness of breath and a low abdominal pain that radiated into the upper abdominal epigastric area, with nausea and vomiting and associated weakness on two occasions. Medications had been taken through the evening of the day before admission. Progressive weakness, anorexia and nausea continued on the day of admission, but she did not vomit again. The chest and neck pains had eased the morning of admission, but dull epigastric discomfort persisted. There had been no cough or evidence of respiratory infection and no chills, fever, sweating or diarrhea.

What with these multiple illnesses, the family had become fairly astute in clinical assessment and they judged the changes in the morning preceding admission to indicate substantial illness and progressive worsening. The referring physician therefore suggested immediate transfer by ambulance. However, the family elected to transport the patient themselves and thereby delayed admission for two and a half hours.

On physical examination the patient was observed to be tremendously large for her body build. She was lethargic and dazed, but with repeated stimuli she seemed oriented; and although she spoke slowly and in a dazed manner, her answers to questions were corroborated as being correct in content. Blood pressure was 90/55 mm of mercury. The pulse was 84 and regular. The skin was flushed and generally dry. Rectal temperature was 35.5°C (95.9°F), and not until 14 hours later did it reach 37°C (98.6°F). Tachypnea and hyperpnea and respirations of Kussmaul type were noted. The neck was supple. The pupils were medium sized and reacted sluggishly. The lungs were clear to auscultation. No abdominal tenderness or masses were defined and there were no signs of peritoneal irritation. The lower extremities were not edematous. Femoral pulses were moderately decreased in force and the pedal pulses were absent.

Shortly after admission the patient was in a very deep sleep, responding only slightly to stimulation; and subsequently she was stuporous and finally comatose. Laboratory data were as follows: Hemoglobin 14 gm per 100 ml of blood and packed cell volume was 42 per cent. Leukocytes numbered 31,000 per cu mm with neutrophils 84 per cent, non-segmented neutrophils 3 per cent, monocytes 3 per cent and lymphocytes 10 per cent. Blood urea nitrogen was 36 mg, blood sugar 167 mg and serum phosphorus 8.5 mg per 100 ml.

Table 1 shows initial and subsequent levels for other pertinent laboratory data, particularly as regards electrolyte and acid base balance. The serum examination for acetone at the time of admission showed no ketoacidosis and there was no acetonuria. Urinalysis showed a pH of 6.0, specific gravity 1.015, 1 plus sugar content, and 1 plus proteinuria. There were 8 to 10 erythrocytes per high power field and occasional granular casts. The serum glutamic oxaloacetic transaminase (SGOT) was 58 units, and the alpha-hydroxy

TABLE 1.—*Laboratory Data on Blood with Regard to Electrolyte and Acid Base Balance.*

Date	Time	pH	pCO_2 (mm Hg)	CO_2	Na	K	Cl	P	BUN	Glucose	Lactate	Pyruvate	Lactate Excess	Osmolarity
				(mEq/L)				(mg per 100 ml)			(mM per Liter)			
11-22	3:30 p.m.	6.83	25	9.9	137	4.6	104	8.5	36	167	24	0.23	19.5	307
	8:40 p.m.	6.99	37	....	......	....	......	....	....	......	17	0.26	15.9	......
11-23	7:00 a.m.	7.40	41	....	142	3.4	101	2.9	....	225	....	......	......	315
	2:00 p.m.	7.47	....	....	......	....	......	....	....	76	....	......	......	......
11-24	6:30 a.m.	7.46	....	....	141	3.2	......	....	25	266	....	......	......	303
11-26	6:30 a.m.	......	....	....	134	3.5	......	....	19	210	....	......	......	292
12-1	6:30 a.m.	......	....	....	141	3.7	......	....	....	175	....	......	......	......

butyric dehydrogenase was 213 units. Cultures of stool, urine, blood and material swabbed from the throat did not grow pathogens. A week after admission the SGOT was 76 units with normal bilirubin and normal alkaline phosphatase. A serology test for syphilis was negative. Calcium phosphorus determinations at this time were within normal range, as were subsequent 17 ketosteroids and 17 ketogenic steroid levels. Urinary catechol levels were within normal range the eighth day after admission, and at that time the urine sodium and potassium excretion determinations over a 24 hour period also were normal.

The patient had been admitted at 2:15 p.m. and vigorous sodium bicarbonate therapy was begun at about 5:00 p.m. She was given sodium bicarbonate along with 1,000 ml of 5 per cent dextrose and saline solution at the beginning and then was also given sodium bicarbonate frequently by direct intravenous therapy. In the first seven hours 290 mEq of sodium bicarbonate was given intravenously and by the end of 14 hours a total of 404 mEq had been given. Shortly after intravenous bicarbonate therapy was begun, the first of two intravenous infusions of methylene blue was given—2.2 mg per kg of body weight at approximately 5:20 p.m. Mephentermine (Wyamine®) was given at first to maintain blood pressure, but as the pressure was subsequently maintained by the other fluid therapy, no other specific agent was used for this purpose after the first hour. Oxygen was administered by tent early. At 9:30 p.m. an additional intravenous infusion of methylene blue, 2.2 mg per kg of body weight, was given at a steady rate over the course of an hour.

The comatose state continued through approximately 6:30 p.m. and then progressive clearing ensued, the patient being considerably more alert by 10:00 p.m. She was at this time talking and asking questions, although she was confused as to time and place. At 9:15 p.m. the blood pressure was 160/90 mm of mercury and the pulse rate 120. Hyperpnea and warm dry skin continued.

At 6:45 the following morning moderate acetonuria was noted for the first time, but no glycosuria. It was felt that a phase of ketoacidosis was beginning and therapy was so directed. By noon that day, 22 hours after admission, the patient had 2 plus glycosuria and a trace of acetonuria. By evening, acetonuria and glycosuria had cleared. Blood sugar was 76 mg per 100 ml. Very small amounts of insulin were necessary therapeutically. X-ray films of the chest made early and subsequently showed no focal effusions or evidence of infiltration or congestion. An electrocardiogram was not specifically abnormal, but was compatible with a metabolic disturbance.

The patient steadily improved. At the time of discharge she was fully ambulatory with diabetes controlled with 25 units of insulin. The blood pressures remained in the range of 160/190 to 190/110 mm of mercury. Subsequent gastrointestinal roentgenographic studies showed no abnormality except minimal diverticulosis of the sigmoid colon and an electrocardiogram did not show myocardial infarction.

Discussion

The problem of a patient with clinically severe acidosis confirmed by immediately available laboratory studies showing a pH of 6.83 and a carbon dioxide content of 9.9 mEq per 100 ml of blood, and with no acetonuria or acetonemia demonstrable, should arouse suspicion of possible lactic acidosis among the other differential diagnostic considerations. Lactic acid determinations are often not readily available in many facilities. If early vigorous correction of the acidosis by administration of bicarbonate is to be followed by a possibly more definitive treatment such as intravenous infusion of methylene blue, it would be desirable to have some rapid test which would strongly suggest the acidosis was secondary to substantial lactate excess. Tranquada[4] noted a two- to three-fold elevation of serum phosphorus levels when the blood urea nitrogen is only moderately elevated in many instances of lactic acidosis. The phosphorus level of 8.5 in the present case confirmed the suspicion of probable lactate excess. The remaining serum of the specimens taken at 3:30 and 8:40 p.m. (See Table 1) was frozen and therapy was directed on a presumption of lactic acidosis. The lactate levels were subsequently determined by two methods, the colorimetric method described by Barker and Summersun (Journal Biological Chemistry, 138:535, 1941), and the enzymatic method of Loomis (Journal of Laboratory and Clinical Medicine, 57:966-969, June 1961).

In the present case survival from a usually fatal illness may have been owing to early vigorous bicarbonate therapy, to methylene blue treatment or to the combination of the two. Reported treatment in other cases with bicarbonate has usually not been successful. It might be quite important, therefore, to make a presumptive diagnosis on the basis of clinical and laboratory findings of severe acidosis without ketosis and elevated phosphorus, and to begin treatment accordingly without immediate confirmation of elevated lactate levels, unless facilities for determining lactate content of the blood are at hand.

Daughaday and coworkers[2] have reported adequately documented cases of nonketotic acidosis in diabetic patients. The patients were not taking phenformin. Generally the response in those cases to therapy with sodium bicarbonate was rapid and good. The variability in the elevation of lactate and the clinical correlation with the degree of acidosis in coma has been apparent to many investigators.[3] The patient in the present case, who had a history of hypertension, had clinical symptoms of severe acidosis with rapid progression and apparent deterioration associated with hypotension. It was because of the clinical condition and a reduction of pH to 6.83 that the vigorous therapy was undertaken. Retrospectively one wonders if improvement might not have been equally good with large amounts of bicarbonate along with other supportive measures, without methylene blue. However, from review of the literature it is apparent that in cases in which there is derangement of the acid base balance and an associated clinical deterioration or considerably altered status sensorium, the patient usually dies. Moreover, in the present case, on suspicion that there might be a pharmacological anoxic derangement of the normal metabolic or oxidative pathways, bicarbonate was given early to correct the acidosis; and then methylene blue was added to provide an alternate oxidative system as had been outlined by Tranquada and coworkers.[5]

Perhaps the favorable outcome in the present case was owing to the early beginning of vigorous bicarbonate therapy, although Tranquada[6] and Bernier[1] reported early treatment without success. The arterial pH of 6.83 in the present case was among the lowest reported in similar cases, the lowest among cases in which there was so severe a clinical deterioration and the patient lived.

Generic and Trade Names of Drugs

Phenformin—*DBI.*
Hydrochlorothiazide—*Hydrodiuril.*
Reserpine—*Serpasil.*
Meclizine dihydrochloride and nicotinic acid—*Antivert.*
Trihexyphenidyl—*Artane.*
Methentermine—*Wyamine.*

REFERENCES

1. Bernier, G. M., Miller, M., and Springate, C. S.: Lactic acidosis and phenformin hydrochloride, J.A.M.A., 184:43-46, 1963.
2. Daughaday, W. H., Lipicky, R. J., and Raskinski, D. C.: Lactic acidosis as a cause of nonketotic acidosis in diabetic patients, New Engl. J. Med., 267:1010-1014, 1962.
3. Huckabee, W. E.: Lactic acidosis, Amer. J. Med., 30:840-848, 1961.
4. Tranquada, R. E.: Lactic acidosis, Calif. Med., 101: 450-461, 1964.
5. Tranquada, R. E., Bernstein, S., and Grant, W. J.: Intravenous methylene blue in the therapy of lactic acidosis, Arch. Int. Med., 114:13-25, 1964.
6. Tranquada, R. E., Bernstein, S., and Martin, H. E.: Irreversible lactic acidosis associated with phenformin therapy, J.A.M.A., 184:37-42, 1963.

Disseminated Tuberculosis Of Bone

EDWIN S. WILSON, JR., CAPTAIN, MC, USA
AND EDWARD G. WHITING, JR., CAPTAIN,
MC, USA, *San Francisco*

Disseminated bone tuberculosis is not often reported. O'Malley and coworkers[13] reviewed the world literature and noted that although over 500 cases had been reported, only 60 had been carefully documented by strict pathologic and bacteriologic criteria. Reviewing 36,372 unselected admissions for tuberculosis, McTammany and coworkers[12] reported that osteoarticular tuberculosis was present in 3.8 per cent of patients, and that only 4.6 per cent of this latter group presented with multiple lesions of the skeletal system. Although statistically unsubstantiated at present, there appears to be a trend toward a decreasing incidence of skeletal tuberculosis, reflecting both the control of bovine tuberculosis in the United States and the development of effective anti-tuberculous agents.[6,11,12]

From Letterman General Hospital, San Francisco.

Submitted 7 June 1966.

This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

Reprint requests to: Radiology Department, Letterman General Hospital, San Francisco 94129 (Captain Edwin S. Wilson, Jr.).

In 1920 Jungling described a group of patients with cyst-like lesions of the small bones of the hands and feet and negative tuberculin skin tests. He called this disease osteitis tuberculosa multiplex cystica, but eight years later renamed the entity osteitis tuberculosa multiplex cystoides to emphasize the pseudo-cystic nature of the lesions. Ellis[4] in 1939 suggested that the cases reported by Jungling were actually examples of osseous sarcoidosis, and this apparent inconsistency generated much confusion in the literature concerning terminology and roentgenographic manisfestations of skeletal tuberculosis. Alexander and Mansuy[1] in 1950 reported a case of skeletal tuberculosis with multiple bone involvement, and coined the term disseminated bone tuberculosis to describe those cases of multiple bone tuberculosis in adults, with or without a cystic appearance of the lesions roentgenographically. Two years later Komins[9] elaborated on the subject and suggested that those tuberculous lesions of a cystic nature in children be called multiple pseudo-cystic tuberculosis of bone, and that the term disseminated bone tuberculosis be reserved for adults with multiple lesions, as originally proposed by Alexander and Mansuy. The lesions of sarcoidosis were designated as osteitis multiplex cystoides sarcoidosa.

The purpose of the present report is to present a patient with disseminated bone tuberculosis in whom neurologic deficit developed in all four extremities during the period in hospital, but who responded favorably to prompt medical and surgical therapy.

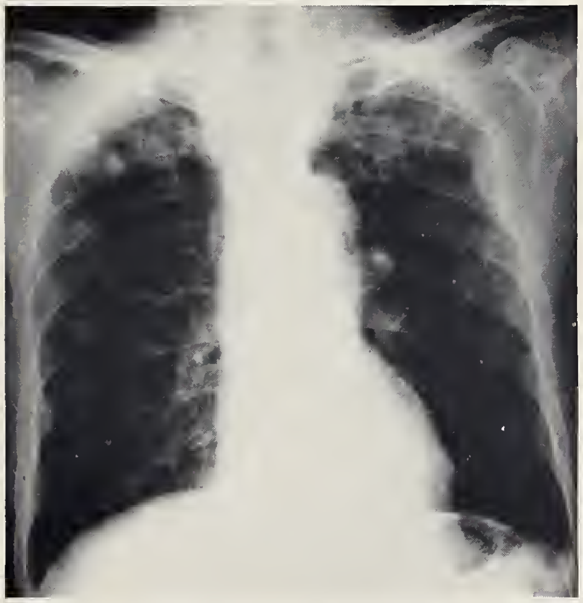


Figure 1.—The x-ray film on admission demonstrating bilateral pulmonary densities and a destructive process evident in the left fourth rib.

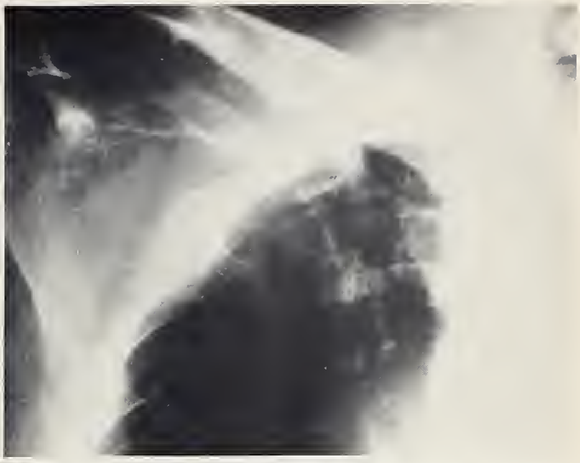


Figure 2.—Bone detail film demonstrating a destructive focus in the right second rib. Similar lesions were noted in the left fourth and twelfth ribs and the right eleventh rib.

Report of a Case

The patient, a 62-year-old Filipino who had entered the United States from the Philippine Islands in May of 1964, was well until, in December of that year, intermittent interscapular pain developed. The pain was aggravated by motion. He was seen at Letterman General Hospital on 25 June 1965, and an x-ray film of the chest showed bilateral pulmonary densities and multiple lytic rib lesions. Inquiry elicited no family history or history of exposure to tuberculosis, and the physical examination was within normal limits with the exception of minimal tenderness over the interscapular region.

X-ray studies of bones showed destruction of the sixth cervical vertebra, probable involvement of the fifth cervical vertebra, and involvement of the disc between the fifth and sixth cervical vertebrae.

On 4 July 1965 the patient had a negative reaction to purified protein derivative (PPD) No. 1. However, six days later there was positive reaction to the intermediate strength PPD intradermally. Numerous septum cultures were negative for acid-fast bacilli. On 12 July an excisional biopsy of the lesion in the left fourth rib showed caseating granuloma as well as numerous acid-fast bacilli within the specimen. Subsequent cultures of material from the rib lesion yielded acid-fast bacilli that were morphologically and histochemically consistent with mycobacterium tuberculosis.

Therapy with isoniazid, para-amino salicylic ascorbate (PAS-C), and streptomycin was instituted, and a cervical collar was utilized to prevent spinal cord compression in view of the cervical spine lesion. Despite these measures, transient weakness of his right arm developed. At that time it was decided that spinal fusion would be carried out but before it could be done, paresis of all extremities developed, together with bilateral ankle clonus and Babinski reflexes, and bladder and bowel dysfunction. Skeletal traction was instituted and on 13 September fusion of the fourth to seventh cervical vertebrae was performed. The patient progressed satisfactorily, and on 4 October was ambulatory about the hospital. On 14 October he was sufficiently well to be discharged from the hospital with prescriptions of isodiazid, PAS-C and pyridoxine, and up to the time of this report he remained well.

Clinical Findings

Skeletal tuberculosis is invariably due to hematogenous dissemination of the bacilli from primary sites elsewhere within the body. Children and young adults appear to be particularly susceptible to skeletal involvement and in the colored races there is a higher incidence of multiple bone involvement, suggesting increased susceptibility to hematogenous spread of the infectious process.[7,9] In nearly all cases there are demonstrable pulmonary lesions, although cases have been reported without apparent lung involvement.[1,6,8,10,13] It is in these latter instances that a diligent search should be made for other visceral sites of the primary infection, such as the genitourinary tract.

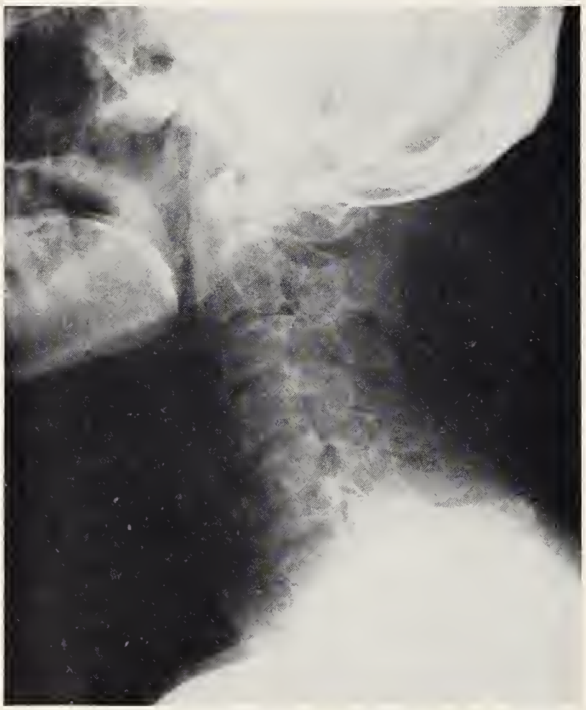


Figure 3.—X-ray film of lateral cervical spine demonstrating the destructive process of the sixth cervical vertebra as well as apparent involvement of a portion of the fifth vertebra and the disc between the fifth and sixth.

Patients with disseminated bone tuberculosis may present with pain, swelling, fever, lymphadenopathy, draining sinuses and neurologic signs secondary to cord compression. In the latter instance, the prognosis is grave. Bosworth and coworkers[3] reviewed a series of 122 patients with paraplegia secondary to skeletal tuberculosis, and noted an overall mortality of 56.5 per cent. Of further prognostic significance was the fact that the mortality rate among patients with complete paraplegia was 69 per cent, whereas only four per cent of the patients with paresis died. In this group of patients the heralding sign of the need for surgical intervention was the development of ankle clonus, as further neurologic decompensation rapidly followed.

Roentgenographic Findings

In adults with disseminated bone tuberculosis the lesions usually involve the bones of the axial skeleton, the most common site being the vertebrae of the thoracic spine.[5,12,13] The flat bones of the pelvis and ribs and the proximal tubular bones are less commonly affected, and there is rarely involvement of more than four sites in adults.

The individual lesions of disseminated bone tuberculosis are characterized by the presence of lytic areas, usually beginning in the cancellous portion when tubular bones are involved, with a minimum of periosteal reaction. With some of the smaller and more indolent lesions, a rim of sclerosis about the lesion may rarely be visualized.[9] More advanced lesions may produce cortical erosion, and it is these areas which may appear cystic or multilocular. Concurrently with the cortical destructive process, a smooth periosteal reaction may occur which may give the impression of an expansile destructive process within the bone. Sequestra are rare. In the spine, involvement of the intervertebral disk is characteristic. Soft tissue reaction about the lesion may be evident, and this is especially noteworthy with rib lesions, where the extra-pleural density is contrasted against the air-filled lungs, and also with para-spinous masses produced with vertebral lesions. Healing is characterized by disappearance of the destructive foci, and by gradual restitution of the normal trabecular pattern of bone.

Differential Diagnosis

To be considered in differential diagnosis in cases of multiple destructive lesions of bone, in addition to disseminated bone tuberculosis, are multiple myeloma, metastatic malignant disease, the reticuloendothelioses, including eosinophilic granuloma, the lesions of hyperparathyroidism and osteomyelitis of other than tuberculous origin, such as coccidioidomycosis and other fungal diseases. The presence of pulmonary lesions may provide a useful clue to the diagnosis; however, the ultimate diagnosis rests with histologic demonstration of the caseating granuloma and identification of the organism with appropriate bacteriologic and histochemical techniques.

Treatment

Therapy of this disease turns upon adequate administration of chemotherapeutic agents and such surgical procedures as may be indicated by the scope of the disease. Although various regimens of therapy are advocated, the general consensus is that a minimum of two agents is indicated, and that treatment should be continued for at least 24 months, and longer if indicated by the course of the disease.[2,5] Hodgson and Stock[5] proposed anterior spinal fusion as the ideal surgical intervention, and advocated doing it as soon as the diagnosis of spinal tuberculosis is made. The lesion may be curretted and drained at the time of operation, and in their experience patients have been able to resume normal function in four to six months. Then roentgenographic examination should be done every four to six months until evidence of healing is noted.

Summary

A case of disseminated bone tuberculosis has been presented, along with the pertinent clinical and roentgenographic findings. Multiple destructive lesions of bone warrant suspicion of primary tuberculous lesions elsewhere. Precise bacteriologic and histochemical studies are necessary to establish the diagnosis. Surgical intervention should be considered in selected cases.

REFERENCES

1. Alexander, G. H., and Mansuy, M. M.: Disseminated bone tuberculosis with case report, Radiology, 50:839-843, 1950.

2. Bosworth, D. M.: Treatment of tuberculosis of bone and joint, Bull. N. Y. Acad. Med., 35:167-177, 1959.

3. Bosworth, D. M., Pietra, A. D., and Rahilly, G.: Paraplegia resulting from tuberculosis of the spine, J. Bone and Joint Surg., 35-A:735-740, 1953.

4. Ellis, F. A.: Jungling's "osteitis tuberculosa multiplex cystoides" is not cystic tuberculous osteitis, Acta Med. Scand., 104:221-224, 1940.

5. Hodgson, A. R., and Stock, F. E.: Anterior spine fusion for the treatment of tuberculosis of the spine, J. Bone and Joint Surg., 42-A:295-310, 1960.

6. Hunt, D. D.: Problems in diagnosis osteo-articular tuberculosis, J.A.M.A., 190:95-98, 1964.

7. Jacobs, P.: Osteo-articular tuberculosis in colored immigrants: a radiological study, Clin. Rad., 19:59-69, 1964.

8. Kelley, W. H., and Sailer, S.: Disseminated tuberculosis of the skeleton, Am. Rev. Tuberc., 42:691-696, 1940.

9. Komins, C.: Multiple cystic tuberculosis: a review and a revised nomenclature, Brit. J. Rad., 25:1-8, 1952.

10. Lyford, J.: Disseminated tuberculosis of bone with multiple localizations in the skeleton: a report of two proved cases, J. Bone and Joint Surg., 25:453-460, 1943.

11. Marwah, V.: The changing pattern of osteo-articular tuberculosis, J. Indian Med. Assoc., 38:18-20, 1962.

12. McTammany, J. R., Moser, K. M., and Houk, V. N.: Disseminated bone tuberculosis, Amer. Rev. Resp. Dis., 87:889-895, 1963.

13. O'Malley, B. W., and Zeft, H. J.: Disseminated bone tuberculosis without pulmonary manifestations, Amer. J. Med., 38:932-936, 1965.

Myeloproliferative Disorder And Tuberculosis

IRVIN HERMAN, M.D., *Oakland*

ALTHOUGH the association of tuberculosis and hematologic disease has long been known, there is no supported understanding of their interrelationship. Clinically, the serologic abnormalities may be coexistent with or stimulated by the tuber-

---

From Highland-Alameda County Hospital.

Submitted 21 March 1966.

Reprint requests to: Respiratory Function Laboratory, Department of Medicine, Stanford Medical Center, 300 Pasteur Drive, Palo Alto, California 94304 (Dr. Herman).

culous infection, and they can be so striking that the diagnosis of disseminated tuberculosis is obscured,[8] as it was in the case here reported. Cases of this kind stimulate recurrent consideration of a possible pathogenic relationship between hematologic disorders of unknown cause and the infection whose characteristic lesion is not fully understood.[4]

Report of a Case

A 67-year-old Spanish woman was first admitted to Highland-Alameda County Hospital in May 1963 with right lower lobe pneumonia which responded to penicillin. Anemia and hepatosplenomegaly were noted.

Results of hematologic studies were as follows: Hematocrit 29 per cent; leukocytes 6,000 per cu mm of blood with a differential of 41 per cent segmented forms, 27 per cent banded neutrophils, 7 per cent metamyelocytes, 7 per cent myelocytes and 20 per cent lymphocytes. There were 230,000 platelets per cu mm, 3.4 reticulocytes per 100 red cells and three nucleated red cells per 100 white cells. The red cells showed stippling and moderate anisocytosis and poikilocytosis. Cell indices were microcytic, hypochromic. Three attempts at obtaining bone marrow were unsuccessful. A bone biopsy showed hypoplastic marrow with moderate fat and fibrous tissue. An x-ray survey of bones was interpreted as showing a sclerotic bone pattern. A provisional diagnosis of agnogenic myeloid metaplasia was made.

The patient was readmitted in September 1963 with right lower lobe pneumonia. The hematologic status was not changed from that at the previous admission. Antibiotics again were effective against the pneumonia and the patient was then observed intermittently in the clinic.

She entered the hospital again in May 1964 with fever, anasarca, dyspnea and pyuria. Urine cultures grew E. coli, and A. areogenes. She did not respond to antibiotics, her condition deteriorated, hematochezia developed and she died. At this time hemoglobin was 5.6 gm per 100 ml of blood, leukocytes varied between 3,600 and 5,500 per cu mm with 34 per cent segmented forms, 38 per cent bands, 11 per cent metamyelocytes, 16 per cent lymphocytes and 1 per cent basophils. There were four nucleated red cells per 100 white cells.

At autopsy bone marrow sections showed fibrous tissue containing epithelioid granulomata with acid-fast organisms (Figures 1, 2). Similar granulomata were also seen in the lung, liver, spleen and one adrenal gland. There was prominent myelopoiesis in the spleen, and scattered areas of myelopoiesis were seen in the liver.

Lymph nodes showed confluent granuloma which contained many acid-fast bacilli. Other findings included chronic pyelonephritis, rheumatic aortic valvular disease with myocardial hypertrophy, and chronic cholecystitis with calculi.

Discussion

Laboratory, x-ray and physical findings in this patient supported the diagnosis of agnogenic myeloid metaplasia and delayed the diagnosis of disseminated tuberculosis until autopsy. The presence of granuloma containing acid-fast organisms

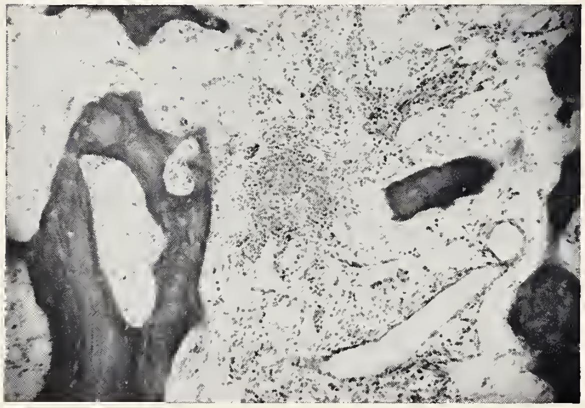


Figure 1.—Photomicrograph of postmortem bone biopsy. Hematoxylin and eosin stain (×100). A granuloma is seen in the center of the field. The remainder of marrow shows hypoplasia of cellular elements with diffuse fibrosis.

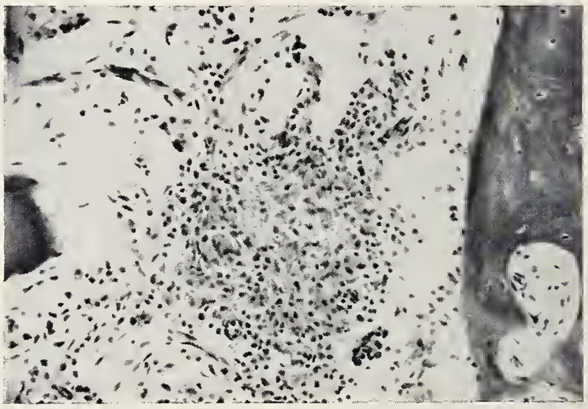


Figure 2.—Photomicrograph of postmortem bone biopsy. Hematoxylin and eosin stain (×400). The granuloma demonstrates necrosis, giant cell formation and epithelioid proliferation. Acid-fast organisms were demonstrated in this lesion by appropriate stains. Surrounding marrow is hypoplastic and fibrosed.

in the marrow and myelopoiesis in the liver and spleen prompts speculation as to possible causal relationship.

Usually with tuberculous infections there are either no serologic changes[9] or moderate lymphocytosis.[12] Occasionally, however, there is leukemoid reaction or pancytopenia in which the marrow is normal, hypoactive or fibrosed.[8] The leukemoid reaction may be indistinguishable clinically or on bone marrow examination from other types of leukemia. While tuberculosis can also occur with leukemia, this relationship is considered coincidental.[7,11] However, there is an implied question about the mutual effects these diseases may have on their individual courses.[4]

The relationship of tuberculosis to the pancytopenias, especially with myelofibrosis, appears more complicated. As in the case reported here, tuberculosis may appear with a myeloproliferative disorder so that it is impossible to determine if the infection was etiological, coincidental or stimulated by the blood abnormality.[1,8] Had antemortem studies in this patient showed the tuberculous involvement of the bone marrow and the extra-medullary hematopoiesis, anti-tuberculosis therapy would have been given and the response to it might have helped determine this relationship.

It is interesting that all the myeloproliferative diseases from polycythemia vera to agnogenic myeloid metaplasia and myelogenous leukemia have been reported to occur with tuberculosis.[5] In first cases of polycythemia reported (by Rendu and Widal in 1892) the patient had tuberculosis.

In a review of this association, prompted by their experience with three cases of idiopathic myeloproliferative syndromes with tuberculosis, Andre, Schwartz and Dameshek[1] proposed these possible relationships: 1. The association may be coincidental. 2. The hematologic disorder may favor the development of tuberculosis. In view of the findings of tuberculous lesions within the bone marrow, it is possible that the tuberculosis bacilli may thrive in the changed marrow. Defects in immune mechanisms which accompany many blood disorders may enhance an already present tuberculous infection. 3. Treatment of blood disorders may increase susceptibility to tuberculosis by the use of agents that affect the immune mechanisms such as steroids, alkylating agents and x-ray. 4. Tuberculosis may cause the blood disease. This is suggested because infection may be antecedent and there may be failure to demonstrate leukemic lesions at autopsy in patients with blood diagnoses antemortem. Tuberculosis has been shown to cause fibrotic lesions and myeloid metaplasia in splenic foci.[4] Experimental studies demonstrate that changes in growth patterns of cells and tissues can be caused by the tubercle bacilli or their products.[2,10] This suggests some factor of the tubercle bacillus may be common to other suspected etiologic agents which cause abnormal myeloproliferation. 5. The coexistence of the two disorders may be an interplay of the above factors.

Whatever the relationship, it is important to acknowledge this undefined coexistence. In certain hematologic disorders, especially when there is pancytopenia or myelofibrosis, attempt should be made to determine whether tuberculosis is also present.

There may be no clues to the underlying infection, as in the case reported here. In four cases reported by Mead and Hayhoe,[8] the patients had pancytopenia, high fever, sweating, weight loss and palpable spleen. In the present case the patient had recurrent pneumonia. Such clinical combinations should suggest tuberculosis, particularly when dealing with susceptible racial groups or where there is a history of past infection or exposures. Besides routine studies, bone marrow aspirate should be cultured. Since hepatic involvement is a frequent concomitant of hematologic involvement, percutaneous liver biopsy specimens should be examined for granulomas and cultured for tuberculosis organisms.

If no infection is found but suspicion remains high, serious consideration should be given to a therapeutic trial of anti-tuberculous therapy.

Summary

A myeloproliferative disorder in an elderly woman and diagnosed as agnogenic myeloid metaplasia. At autopsy, unsuspected granulomas that contained acid-fast organisms were found in bone marrow sections as well as in many viscera. There were also areas of myelopoiesis in the spleen and liver.

The frequent coexistence of tuberculosis and myeloproliferative diseases is poorly understood.

The tuberculous infection may present only nonspecific clinical findings or be completely masked by the hematologic disorder. To make the diagnosis of a potentially treatable cause of myeloproliferation, it is suggested that in addition

to routine tuberculosis evaluation, biopsy specimens of liver and bone marrow aspiration be cultured for acid-fast organisms. A clinical trial of anti-tuberculosis agents may be indicated.

REFERENCES

1. Abbott, J. D., and Lew, A. J.: Leukemia and pulmonary tuberculosis, Lancet, 2:917, November 1957.

2. Andre, J., Schwartz, R., and Dameshek, W.: Tuberculosis and myeloid metaplasia, J.A.M.A., 178:1169, December 1961.

3. Crail, H. W., Alt, H. L., and Nodlar, W. H.: Myelofibrosis associated with tuberculosis, Blood, 3:1420, December 1948.

4. Dameshek, W., and Gunz, F.: Leukemia, Second Edition, Grune & Stratton, New York, 1964.

5. Feldman, W. H., and Stasney, J.: Leukemoid response of tuberculosis rabbits to administration of tuberculin, Amer. J. Med. Sci., 193:28, January 1937.

6. Korn, R. J., Kellow, W. F., Heller, P., Chornet, B., and Simmerman, H. J.: Hepatic involvement in extrapulmonary tuberculosis, Amer. J. Med., 27:60, July 1959.

7. Lowther, C. P.: Leukemia and tuberculosis, Ann. Int. Med., 51:52, July 1959.

8. Medd, W. E., and Hayhoe, F. G. E.: Tuberculous miliary necrosis with pancytopenia, Quat. J. Med., 24:351, October 1955.

9. Muller, G. C.: Clinical significance of blood in tuberculosis, New York, Commonwealth Fund, 1943.

10. Sabin, F. R., Doan, C. A., and Forkner, O. E.: Studies on tuberculosis, J. Exp. Med., Suppl. 3, 1, 1930.

11. Twomey, J. J., and Leavell, B. S.: Leukemoid reactions to tuberculosis, Arch. Int. Med., 116:21, July 1965.

12. Wintrobe, M. M.: Clinical Hematology, Fifth Edition, Lea & Febiger, Philadelphia, 1961.

Acute Cadmium Fume Poisoning in Welders—A Fatal and a Nonfatal Case in California

HECTOR P. BLEJER, B.SC., M.D., D.I.H., AND PAUL E. CAPLAN, A.B., B.S., M.P.H., *Los Angeles*, AND ARTHUR E. ALCOCER, A.B., M.P.H., *Berkeley*

OCCUPATIONAL EXPOSURE to cadmium is certainly as old as man's use of metals, and likely dates back more than four thousand years, into the bronze age. Even though Aristotle recorded his observations in the Fourth Century, B.C., and though acute pulmonary illness and death from exposure to cadmium oxide fumes have been described repeatedly in the medical literature, it is still a diagnosis that is overlooked. To the welder, cadmium presents an often unsuspected and probably a greater hazard than any other metal. Freshly generated cadmium oxide fumes are so toxic that they are reported to have been considered for use in chemical warfare.[8]

Reports of Cases

CASE 1. After less than two hours' brazing* with a cadmium-silver alloy, a 35-year-old white male welder complained of feeling ill. He had been brazing indoors, without any supplementary dispersing or exhausting ventilation or respiratory protective device. Although malaise continued, he finished his shift and went home, after an estimated maximal brazing fume exposure time of two and a half hours of the six and a half he had worked that day. The next day he felt worse and did not go back to work. By then severe cough and chest pain had developed, with shortness of breath, increased malaise and fever. A relative noticed that the welder's face looked blue. An expert welder, the patient attributed all of these symptoms to "welder's fever," which he had had before. Finally, one day later, he was persuaded by a relative to see a physician. As the patient did not know that the silver brazing alloy contained cadmium, he could not so inform the physician, who obtained a history of possible welding fume inhalation.

On examination, the patient was observed to be coughing considerably, but no cyanosis was noted. The pulse rate was 100 and blood pressure 125/80 mm of mercury. The temperature was not recorded. The breath sounds were harsh, but no adventitious sounds were noted. A diagnosis of chemical bronchitis was made. A tetracycline antibiotic was prescribed, together with an antitussive with codeine, plus the use of a vaporizer and increased intake of fluids. The patient was advised to return one or two times within the next five to seven days or as he felt necessary. Back at home, the welder felt improved during the next day. However, the following day he was found dead in his bedroom early in the morning.

The total time between exposure to the cad-

Submitted 5 April 1966.

Reprint requests to: Bureau of Occupational Health, California State Department of Public Health, 1930 Beverly Boulevard, Los Angeles 90057 (Dr. Blejer).

*Silver brazing is commonly and mistakenly called "silver soldering" even by welders. Brazing is the process of soldering with a relatively hard to fuse alloy, at temperatures higher than those needed with fusible solders.

TABLE 1.—*Concentrations of Metals (Wet Basis) Noted on Tests of Necropsy Specimens in Case 1, with Normal Values Shown in Parentheses*

Source	*Cadmium*	*Antimony*	*Arsenic*	*Copper*	*Zinc*
Lung (µg/gm)......	4.1 (<0.5-1.3[1])	N.D.	N.D.	3 (0.9 - 2.34[1])	3 (8.6 - 23.4[1])
Liver (µg/gm).....	5.0 (0.6-5.78[1])	N.D.	N.D.	35 (3.2 -22.1[1])	35 (22.0 -100.3[1])
Blood* (µg/gm)..	N.D. (0.0[2])	N.D. (0.0[2])	N.D. (0.02[2])	15 (0.72- 1.25[4])	15 (4.9 - 12.7[4])
Urine* (µg/ml)...	0.5 (0.0[3])	N.D. (0.0[3])	N.D. (0.1[3])	10	10 (0.14- 0.93[5])

The tests were performed by Air and Industrial Hygiene Laboratories of the State Department of Public Health, Berkeley.

N.D.=Not Detected

*Cotter, et al.,[3] cite Cadmium levels in poisoning cases for *blood* ranging from 1.2 to 3.8 µg/gm, and for *urine* ranging from 0.1 to 0.36 µg/ml.

Harmful Exposure Level (urine)[6]=0.1 mg Cadmium/Liter, or 0.1 µg Cadmium/ml.

NOTE: For references, see list at end of article.

mium oxide fumes and death was just under four days. At autopsy, performed the day of death, an abundance of dark fluid was noted in the nares. Among other findings was massive pulmonary edema with extreme pulmonary hemorrhagic congestion. Microscopically, lung tissue showed edema, bronchial de-epithelialization, with infiltration of large cells in the small bronchi and the alveolar septa. Results of polarographic and emission spectrographic analysis of tissues and body fluids for five different elements are shown in Table 1. The composition of the silver brazing alloy used by the patient was as follows: Cadmium, 26 per cent; silver, 47 per cent; zinc, 15 per cent; copper, 12 per cent.

The final diagnoses were: Acute cadmium oxide fume poisoning, cadmium pneumonitis and pulmonary edema due to cadmium.

CASE 2. A 28-year-old white male welder in the same company as the patient in Case 1 was also exposed to the same brazing fumes, but to a lesser degree. Exposure occurred a few days after the first welder's death had become known, and the cause of it suspected. By then certain precautions had been taken: the process had been transferred outdoors, and stationary exhaust ventilation had been provided at the source of the fumes. At the end of three days of silver brazing—after an estimated maximal brazing fume exposure time of nine and two-thirds hours—the patient felt ill and sought medical attention. Seen early that evening at the emergency room of one of the local hospitals, he said that he had been brazing with a cadmium-containing alloy and had begun to have stomach cramps at about 6 p.m. At that time, blood pressure was recorded at 96/50 mm of mercury and oral temperature at 37.1°C (98.8°F). He was admitted to hospital immediately. On closer questioning, the welder gave a history of cough, shortness of breath, generalized malaise, nausea, diarrhea and abdominal cramps, all of sudden onset.

On physical examination the patient was alert and cooperative and apparently in no distress. No cyanosis was noted. Blood pressure was 122/66

TABLE 2.—*Results of Tests Done During Hospital Admission* (Case 2)*

Chemical		*Blood Morphology and Serology*		*Urinalysis*	
Serum:		Erythrocytes	..........5.3×10^6/cu mm	Specific gravity	.... 1.016
Protein	...................6.2 gm/100 ml	Hemoglobin	..........13.4 gm/100 ml	pH	 5
Albumin	..........3.9 gm/100 ml	Leukocytes	................13,600/cu mm	Albumin	 0
Globulin	..........2.3 gm/100 ml	Polys.	.... 66 per cent	Sugar	 0
A/G	..................1.7	(Segm.	.......55 per cent)	Microscopic:	
SGOT	....................................124 units	(Nonsegm.	11 per cent)	Erythrocytes	 0
Bilirubin		Eosinos.	.... 7 per cent	Leukocytes	.... many
Direct	..................0.2 mg/100 ml	Lymphos.	.... 25 per cent	Epith.	.... +
Total	....................0.9 mg/100 ml	Not Stated	.... 2 per cent	Casts	 0
			——	Bacteria	 0
		Total	......................100 per cent	Crystals	 0
Blood:					
Cadmium†	............<2 µg/100 ml	Hematocrit	............46.5 per cent		
		Sedimentation rate	........4 mm/hr (corrected)		
Urine:					
Cadmium†	............<1 µg/100 ml	Venereal Disease Research Laboratory	............Nonreactive		

---

*Specimens collected and reported during first day of admission.

†Collected during first day of hospitalization, and reported 11 days later—nine days after the patient's discharge.

TABLE 3.—*Results of Analysis* of Biological Specimens (Case 2)*

Specimen	*Cadmium Concentration*
Blood	0.08 mg Cd/100 ml
Urine	0.05 mg Cd/Liter

The normal value for Cadmium in blood and urine is none.[3,6,7]
Harmful Exposure Limit (urine)[6]=0.1 mg Cadmium/Liter, or 0.1 μg Cadmium/ml.

*Performed by AIH Labs., Berkeley; collected 13 days after exposure, and 10 days after discharge from hospital.

mm of mercury. The only abnormal physical findings were wheezing at the bases of the lungs and mild epigastric tenderness. A diagnosis of cadmium poisoning was made, and, in anticipation of pulmonary edema, positive pressure oxygen therapy was started immediately. General supportive therapy also was carried out. Chest roentgenograms taken the next day showed no abnormality. Data from tests done on the day after admission are shown in Table 2. Blood and urine specimens were sent to an outside laboratory for determination of cadmium content. Eleven days later a report was received showing less than 2 μg of cadmium per 100 ml of blood and less than 1 μg per 100 ml of urine (Table 2).

No clinical or other evidence of pulmonary involvement was noted in the next two days. On the positive pressure oxygen therapy the patient improved dramatically, and he was discharged less than 72 hours after admission and returned to work within ten days of that date. He did not work with any cadmium-containing product and at last report was well. Through the county's Health Department, blood and urine samples were collected 10 days after the patient was discharged from hospital—13 days after his last exposure to cadmium oxide fumes. These specimens were analyzed by the Air and Industrial Hygiene (AIH) Laboratories of the State Department of Public Health for cadmium concentrations, and the results are shown in Table 3.

The discharge diagnosis made was: Acute cadmium oxide fume poisoning.

Work Environment Study

Shortly after the cause of the disease in Cases 1 and 2 was suspected, an industrial hygiene evaluation of the exposures to cadmium oxide fumes during the brazing operations in question was done. It was judged unfeasible and too dangerous to duplicate and evaluate the indoor work operation, for the risk of contaminating the work environment was too great.

Consequently, a study was done only of the outdoor work operation closely simulating the work exposure involved in Case 2. The findings are reported in Table 4.

The maximum acceptable concentration for cadmium oxide fume has been established by the State Division of Industrial Safety to be 0.1 mg per cubic meter of air (mg/M^3). By definition, the maximum acceptable represents "the concentration of fume in which it is considered safe for men to work, whether for brief periods or for full working periods daily for an indefinite time."

Acute cadmium poisoning can occur in two ways, by inhalation of freshly generated cadmium fumes, and by ingestion of cadmium compounds.

Inhalation. In cases of inhalation poisoning, almost invariably the patient is an industrial worker, a high proportion of them welders. The intoxication results from the inhalation of high concentrations of cadmium fumes, typically following heating, welding or burning of cadmium-

TABLE 4.—*Atmospheric Concentrations of Cadmium Oxide Fumes§ Mock-up of Work Operation of Case 2*

Location	*Operation*	*Atmospheric Conc. mg/M^3**	*Remarks*
1. Vertical tube stand, outdoors	Brazing with silver-cadmium alloy	0.14	OBZ† sample, with suction hose approximately one foot from alloy operation.
2. Same as (1)	Same as (1)	0.02	OBZ sample, suction hose approximately 8″ from alloy operation.
3. Same as (1)	Same as (1)	0.01	OBZ sample, suction hose approximately 6″ from alloy operation.
MAC‡		0.10	

*mg/M^3=milligram of cadmium oxide per cubic meter of air.

†OBZ=operator's breathing zone.

‡MAC=maximum acceptable concentration as stated in the General Industry Safety Orders of the California State Division of Industrial Safety.

§Collected by the Bureau of Occupational Health, and analyzed by the Branch Public Health Laboratory California State Department of Public Health, Los Angeles.

containing metals or brazing with silver-cadmium alloys.

Symptoms are those of bronchial and pulmonary irritation. Usually they first appear several hours after exposure, but sometimes they appear immediately, and consist of dryness of the throat, cough, headache, dizziness, fever, chest pain and breathlessness. After 12 to 36 hours the chest pain and the dyspnea become extremely severe and intense cyanosis may develop. Delayed pulmonary edema may develop as late as 12 hours after exposure, and delayed hemorrhagic interstitial pneumonitis may develop as early as four days after exposure.[2,10] Moreover, there may be gastrointestinal symptoms and signs such as those associated with cadmium poisoning from ingestion. If exposure to cadmium fumes is sufficiently severe, death occurs in from four to nine days. Patients who survive usually recover without permanent damage,[2,5,9,10,16] with decreasing intensity of the respiratory distress in eight to 14 days.[13]

Ingestion. The acute symptoms of cadmium poisoning by ingestion are those of severe gastroenteritis. They resemble those of food poisoning—nausea, abdominal distress, severe vomiting, diarrhea and weakness, lasting about 24 hours and followed by complete recovery. However, collapse due to gastroenteritis and dehydration may occur in unusually severe cases. Several outbreaks of "food poisoning" have been traced to contamination of food and drink by cadmium salts released from cadmium-plated food containers or utensils. As such containers are no longer in general use in this country, such cases are now rare.

Differential Diagnosis

Since, as was mentioned earlier, acute cadmium oxide fume intoxication is almost invariably due to an occupational (industrial) exposure, it is imperative to ask for and obtain as precise a work history as possible. Moreover, since the presenting symptoms may be "mixed"—referable to the respiratory and gastrointestinal systems—even after the inhalation of such fumes only, the differential diagnosis will have to include:

Metal fume fever*; polymer fume fever; other occupational causes of acute pneumonitis and/or pulmonary edema**; non-occupational causes of acute pneumonitis and/or pulmonary edema; acute gastroenteritis—viral, bacillary, bacterial toxin; acute gastroenteritis due to ingestion of poisonous animals and plants; and other causes of acute gastroenteritis.

Attention must be drawn to the similarities between the symptoms of early acute cadmium fume inhalation poisoning and metal fume fever ("welder's fever"). The latter is a benign, self-limiting condition, characterized by chills, dry cough, dry throat, fever, nausea, vomiting, headache, fatigue, weakness and chest discomfort. It occurs frequently in welders and in other metal tradesmen a few hours after exposure to and inhalation of fumes of various metals, most commonly zinc.[16] The symptoms usually disappear within a day. The worker who has been unknowingly overly exposed to cadmium fumes may mistake his condition for metal fume fever and not seek medical attention. Moreover, even if after a delay a physician is consulted, the similarities between the two diseases, plus unawareness by the worker and the physician that cadmium was involved, may lead to a wrong diagnosis and the wrong treatment for a condition that is a medical emergency. As a rule of thumb, given the right work history, if the symptoms have lasted for over 24 hours and the chest pain is severe, cadmium fume poisoning should be suspected.

Diagnostic Procedures and Tests

Physical examination of the chest is of little assistance in early diagnosis or prognosis. Chest roentgenographs may show scattered patchy infiltration of the lungs, but these may not appear for up to three or four days after over-exposure. Biochemical tests indicative of tissue destruction or organ dysfunction—serum glutamic oxaloacetic transaminase (SGOT), bilirubin and the like—plus other routine blood and urine tests, are indicated, although they may not contribute much to early diagnosis or prognosis. A good work history plus a high index of clinical suspicion is required, therefore, to identify illness from cadmium fumes.

Fortunately, in a diagnostic sense, cadmium, once incorporated in the body, is retained for long periods. Traces of cadmium have been detected as long as 15 weeks after exposure. It is excreted slowly, via the bile, in the feces.[15] Significant concentrations can be detected in urine and blood at least as long as two weeks after overexposure (Table 3) if sensitive analytical techniques are used—for example, hypopolarography and emission spectrography, but these are elaborate procedures, and results may take a week or longer to be reported.

---

*Also called "welder's fever," "galvanized fever," "foundryman's fever," which may be caused by the fumes of lead, copper, magnesium, mercury, zinc, tellurium and a few others.[16]

**Beryllium, bromine, chlorine, hydrazine, nickel carbonyl, nitrogen oxides, phosgene, phosphine, selenium, zinc stearate, dimethyl sulfate, hydrogen fluoride, ozone.[11,16]

Treatment

Acute poisoning by inhalation of freshly generated cadmium fumes is a medical emergency. Therapy consists of:[4,11,16]

- *Oxygen* with inspiratory phase positive pressure.
- *Strict limitation of activity,* due to the "lag phase" of pulmonary edema, even if no symptoms are immediately apparent, until a reasonable period has passed.
- *Broad spectrum antibiotics*—the tetracyclines or semi-synthetic penicillins—with any sign of pulmonary infection.
- *Nebulized bronchial dilators* for bronchospasm—for example, isoproterenol (Isuprel), epinephrine.
- *Cortisone* intravenously for several days, followed by steroids by mouth in more severe cases.
- *Nebulized non-irritant bronchial detergents* to increase mucus excretion.
- *Analgesics* for chest pain. Contraindicated because of pulmonary edema are morphine and opiates and respiratory depressant drugs. Digitalis is also contraindicated, since pulmonary edema of this type is not of cardiac origin.
- *Calcium ethylenediamine tetraacetic acid* (EDTA, Edathamil), a chelating agent, in a dose of 0.5 gram orally every two hours, while awake, for one to two weeks. (This drug is effective, but may produce renal damage; hence, frequent urine and renal function monitoring is necessary.) Due to the nephrotoxicity of the products excreted, Dimercaprol® (BAL, British Anti-Lewisite) is contraindicated here.[13,16]

The importance of holding the patient's activity to a minimum cannot be emphasized enough. Neglect of this injunction has accounted for increased morbidity in many instances. An essential part of the therapy is to prevent the patient from returning to work until the occupational health hazard has been corrected.[11]

Discussion

The industrial hygiene study of the work situation closely duplicating that of Case 2 indicated that under some conditions the maximum allowable concentration (MAC) of 0.1 mg per cubic meter of air for cadmium fumes could be exceeded, and that, therefore, the outdoor work operation could be hazardous to the health and life of any welder doing such brazing (Table 4). From the same study, it can be inferred that, if the operations were conducted inside the building—as they were by the welder in Case 1—with no exhaust ventilation, atmospheric concentrations of cadmium oxide would have exceeded, by at least one order of magnitude, the levels actually measured—that is, they would have been at least ten times the MAC, or at least 1 mg per cm of atmosphere.

In Case 1 a review of the work history and exposure; the onset of symptoms and signs and the clinical history and findings typical of acute cadmium fume poisoning; the pathological findings, both gross and microscopic; and the AIH Laboratory findings of grossly elevated cadmium concentrations in the lungs, as well as in the urine, where the harmful exposure limit was exceeded by five times (Table 1)—all corroborated the diagnoses derived initially from the autopsy and the occupational exposure.

In Case 2 the clinical diagnostic and therapeutic problems were much different. The initial symptoms—given the fact that the cause was suspected from the start by both the welder and the physicians—were essentially those of acute gastroenteritis, with few symptoms referable to the respiratory system. Only a few wheezes were heard at the base of the lungs, and on only one occasion. It is a possibility that the immediate use of oxygen therapy by positive pressure helped rid the lungs of loose cadmium oxide particles which, had they reacted further with the alveolar tissues, might have produced the typical pulmonary complications. From the industrial hygiene study, and from the occupational history, it is known that this patient was most likely exposed to a hazardous concentration of cadmium oxide fumes. It is possible that besides inhaling he also swallowed these fumes, and that the symptoms and clinical findings were due mostly to the ingestion of cadmium oxide particles. Cadmium, however, is not absorbed from the gastrointestinal tract.[2] The fact that in this case the blood and urine showed cadmium 13 days after the last exposure to the brazing fumes, and that gastrointestinal symptoms and signs can be produced by the inhalation of fumes,[2] corroborate the diagnosis of acute cadmium oxide fume inhalation poisoning. This series of events also raises the interesting and therapeutically worthwhile hypothesis that in such cases the judicious and immediate application of oxygen therapy by positive pressure may not only lessen the severity but also shorten the duration of the illness. The elevated serum SGOT and bilirubin (Table 2) point to an acute intracellular liver dysfunction or to massive tissue destruction. Both are known to be produced in the inhalation type of poisoning.[2] The elevated leukocyte count shown in Table 2 indicates an acute inflammatory process also.

In Case 1, the higher than normal concentrations of copper in tissues and fluids, and of zinc in blood and urine (Table 1), cannot be disregarded. No Harmful Exposure Levels for these two metals in blood and urine appear to have been determined.[6] MAC's exist for the fumes of these two metals, but the industrial hygiene study did not test the work atmosphere for them. No conclusions, therefore, can be made as to the significance of their concentrations in the tissues and body fluids of the patient, other than that they were higher than usual as reported. Silver fumes are not known to present a health hazard. Copper and zinc, however, are known causes of metal fume fever.[16] It is known that the presence of mixtures of substances of similar chemical and toxicological properties makes their effects additive in calculating an MAC.[6]

In both Case 1 and Case 2, it can be postulated, therefore, that the effects of the cadmium, copper and zinc fumes were at least additive, and possibly synergistic.

Review and Comments

Deaths from acute cadmium poisoning are extremely rare. In the United States there have been fewer than 20 reported officially in the last 50 years, and only three reported in the medical literature since 1956.[5] Another fact is that every one of these deaths has occurred in industrial workers, especially in welders, and was due to the inhalation of freshly generated cadmium fumes. This hazard is not confined to the spraying, brazing or overheating of alloys or metals containing cadmium. It can also arise from the welding, burning or heating of cadmium-plated steel and other metals.

Domestic industrial cadmium production and shipment increased during 1965.[14] Moreover, it appears that cadmium-containing brazing alloys are being more widely used, not only in industry, but also in high school and university industrial arts and sculpture courses, as well as by hobbyists who make their own jewelry, or repair their own guns and pistols. Since the time that the study of these two cases was reported (January 1966), official reports of another three deaths, and preliminary reports of approximately six other cases, all from acute cadmium oxide fume poisoning, have been received from other states.[8] Another nonfatal case of acute pulmonary edema in a welder brazing with a similar alloy was reported recently from Ontario, Canada.[12]

Summary

Two cases of acute cadmium oxide fume inhalation poisonings—one fatal and the other nonfatal—which occurred recently in California welders are presented. This report also presents (1) a summary of an industrial hygiene evaluation of the work situation atmospheric concentrations of, and exposure to, cadmium oxide fumes of these two welders; and (2) an occupational medical evaluation of the relationship of such exposures to the death and illness of the same workers. Treatment, a short review of the medical and toxicological literature are discussed. As well, mention is made of another 10 cases of the same etiology—including three fatal ones—which have been officially or tentatively reported from other states and Canada since these two California cases were studied and reported.

REFERENCES

1. Blejer, H. P., and Caplan, P. E.: Report of an Occupational Health Study of Exposures to Cadmium Oxide Fumes, Study No. S-1800, State of California Department of Public Health, Bureau of Occupational Health, 1966 (unpublished).

2. Browning, E.: Toxicity of Industrial Metals, pp. 86-87, Butterworths, London, 1961.

3. Cotter, H. L., and Cotter, B. H.: Cadmium poisoning, Arch. Ind. Hyg. & Occ. Med., 3:495, 1951.

4. Current Therapy, Conn, H. F., Editor, p. 766, W. B. Saunders, Philadelphia, 1966.

5. Deichmann, W. B., and Gerarde, H. W.: Symptomatology and Therapy of Toxicological Emergencies, Academic Press, p. 101, N.Y., 1964.

6. Elkins, H. B.: Chemistry of Industrial Toxicology, 2nd ed., pp. 256-257, John Wiley & Sons, N.Y., 1959.

7. Gofman, J. W., de Lalla, O. F., Johnson, G., Kovich, E. L., Lowe, O., Piluso, D. L., Tandy, R. K., and Upham, F.: Chemical elements in the blood of man, p. 80, Semi-Annual Report, Donner Laboratory UCRL-10211, Spring 1962.

8. Handbook of Biological Data, National Academy of Science, p. 52, W. B. Saunders Company, Philadelphia, 1961.

9. Industrial Hygiene Digest, Editorial, Mellon Institute, Pittsburgh, May 1966.

10. Johnstone, R. T., and Miller, S. E.: Occupational Diseases and Industrial Medicine, pp. 277-279, W. B. Saunders, Philadelphia, 1960.

11. Kleinfeld, M.: Acute pulmonary edema of chemical origin, Arch. Env. Health, 10:942-946, 1965.

12. Ontario Department of Health (Canada)—personal communication.

13. Patty, F. A.: Industrial Hygiene and Toxicology, 2nd revised ed., Vol. II, pp. 1016-1017, Interscience Publishers, N.Y., 1962.

14. Schroeder, H. J.: Cadmium in the Fourth Quarter of 1965, Mineral Industry Surveys, Bureau of Mines, U.S. Department of the Interior, Washington, February 1966.

15. Stewart, C. P., and Stolman, A.: Toxicology, Vol. I, p. 209, Academic Press, N.Y., 1960.

16. Thienes, C. H., and Haley, T. J.: Clinical Toxicology, 4th ed., Ch. 21, Lea and Febiger, Philadelphia, 1964.

17. Tipton, I. M., and Cook, M. J.: Health Physics, 9:103-145, 1963.

18. U.S. Public Health Service—personal communications.

19. Vallee, B. L., Wacker, W. E. C., Bartholomay, A. F., and Hoch, F. L.: Zinc metabolism in hepatic dysfunction, New Engl. J. Med., 257:1055, 1957.

MEDICAL STAFF CONFERENCE

Hyperlipemia, Abdominal Pain and Growth Retardation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. LAWRENCE BASSO*: The patient was a nine-year-old white boy admitted for evaluation of hyperlipemia. For two years he has had recurrent left upper quadrant abdominal pain associated with vomiting. On examination elsewhere, shortness of stature, splenomegaly and lipemia retinalis were noted. The blood was pink and the serum grossly lipemic. It separated into creamy supernatant and relatively clear infranatant layers on ordinary centrifugation, a finding consistent with predominant chylomicronemia. The serum triglyceride level four months before the patient was admitted was 1,400 mg per 100 ml. The patient has had no appreciable linear growth since age six and is now shorter than his seven-year-old sister. His learning ability, however, appears to be on a par with that of his other siblings.

On physical examination, he appeared normally developed although of short stature. His height was 117 cm and his weight was 21 kg. Significant negative findings included absence of xanthomata and lipemia retinalis, normal tonsils and absence of significant lymphadenopathy. The spleen was firm and greatly enlarged, the tip extending nearly to the iliac crest. The liver was not enlarged.

Laboratory data were as follows: Hematocrit 28 per cent; leukocytes 3,200 and platelets 80,000 per cu mm of blood and reticulocytes 1 per cent. Red blood cells were microcytic and hypochromic. No abnormality was seen on a smear of sternal marrow. Serum iron was 58 mg per 100 ml and total iron-binding capacity was 495 mg per 100 ml of blood. After a low fat diet and oral iron therapy were begun, the hematocrit was unchanged but the leukocyte count rose to 7,200 per cu mm of blood, platelets to 200,000 and reticulocytes to 4.8 per cent. A guaiac examination of stool initially was positive but reverted to negative when a myoglobin-free diet was given. No stainable fat was present in the stool. Liver function studies were within normal limits as was the creatinine clearance and serum protein-electrophoresis. Calcium was 9.4 mg per 100 ml and phosphorus 4.5 mg per 100 ml of blood.

Results of growth hormone studies were as follows: Following intravenous administration of 0.2 units of insulin per kg of body weight, serum growth hormone level rose from 3 $m\mu g$ per ml to 5 $m\mu g$ per ml. Similar results have been obtained by Kaplan[7] and co-workers in children with growth retardation but with no other laboratory evidence of hypopituitarism. In adults, a rise to at least 15 $m\mu g$ per ml is normal. The oral glucose tolerance test, insulin tolerance test and the Himsworth test (an oral glucose-insulin tolerance test) were all within normal limits. The patient's bone age was retarded to about seven years. X-ray films of the skull showed a normal sella turcica. An upper gastrointestinal series showed no abnormality and the small bowel pattern was normal. An intravenous pyelogram showed a curious anomaly of

---

These studies were carried out on the General Clinical Research Service Ward, University of California, FR-79, provided by the Division of Research Facilities and Resources, USPHS; and were supported by USPHS Grant # HE-06285.

*Trainee in the Cardiovascular Research Institute (NHI Grant #5251).

TABLE 1.—*Per Cent Composition of Plasma Lipoprotein-Lipids*

	Cholesterol Esters	*Free Cholesterol*	*Phospholipids*	*Triglycerides*
Chylomicrons	6	3	7	83
Very low density lipoproteins	18	7	19	56
Patients' lipoproteins (d<1.006)	9	3	9	79

the left kidney which was probably a variant of a horseshoe kidney.

Serum lipoproteins were separated in the preparative ultracentrifuge. The composition of the density less than 1.006 fraction (chylomicrons plus very low density lipoproteins) closely resembled that of pure chylomicrons (Table 1). Very little lipid was present in the low density (1.006-1.063) and high density (1.063-1.21) lipoproteins.

With the patient on a diet containing less than 0.1 gm of fat per kg of body weight daily, the serum triglyceride level fell rapidly and the serum cleared. On the third day of this diet, the triglyceride level was about 200 mg per 100 ml. After the patient had been on the diet for four days, he was given a single meal containing 36 gm of fat. Within 12 hours, the serum triglyceride level rose from 180 mg per 100 ml to about 1,000 mg per 100 ml (Chart 1). Twenty-four hours after the single fat meal, the serum triglycerides were almost 500 mg per 100 ml. After two days, the serum triglycerides were still elevated and visible lipemia extended from two hours to 72 hours after the fat meal.

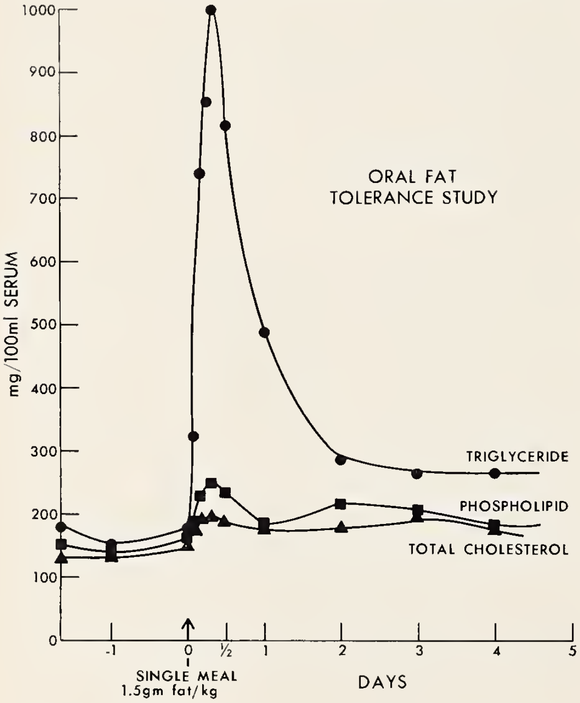


Chart 1.—Effect of a single fat-rich meal on serum lipid levels. (Except for this meal, the patient's diet contained less than 3 gms of lipids daily during the period shown).

Dr. Lloyd H. Smith, Jr.*[1]: This patient and the general problem of hyperlipemia will be discussed today by Dr. Richard J. Havel, Professor of Medicine and Associate Director of the Cardiovascular Research Institute at the University of California Medical Center.

Dr. Richard J. Havel: This patient's disorder is an example of one variety of hereditary hyperlipemia, but some features of his illness have not been previously reported in this syndrome. The condition, first described by Bürger and Grütz,[2] consisted of hyperlipemia with good response to fat restriction. Later, a detailed description was written by Holt[6] and his collaborators at Johns Hopkins. Although eruptive xanthomata were present in the case described by Bürger and Grütz, we have not seen them in this particular variety of essential hyperlipemia. Hepatosplenomegaly is frequently seen, particularly in children. The splenomegaly in the patient presented today is more pronounced than any reported previously to my knowledge. More commonly, the spleen is palpable just below the left costal margin.

Another feature which is also common in other forms of essential hyperlipemia is acute abdominal crisis. Often, recurrent abdominal pain, which is common in childhood and less severe during adolescence, recurs in adult life. Seldom have these abdominal crises in childhood been diagnosed as pancreatitis, and in the patient presented today we have had no clear documentation that he has had pancreatitis. In view of the very large spleen, it is possible that splenic infarcts were the cause of the left upper quadrant abdominal pain.

Growth failure has not been described in this syndrome but the patient in the present case wears the same shoes and the same clothes that he did when he was six years old; his bone age is that of a seven-year-old. At present, we can only speculate on the cause of this growth failure. Possibly, hypersplenism and associated rapid turnover of hematopoietic tissues have taken precedence over utilization of amino acids for somatic growth. In addition, his diet has probably been inadequate. This is shown by the iron deficiency, which cannot be attributed to gastrointestinal blood loss. Leukopenia, which was present on admission, disappeared in association with one or both of two procedures in the hospital—iron therapy and restriction of fat in the diet. Long-term iron deficiency can be associated with leukopenia but is seldom associated with thrombocytopenia of the degree observed here. It is tempting to speculate that phagocytosis of chylomicrons in the spleen may be important in the pathogenesis of the hypersplenism.

---

*[1]Professor and Chairman, Department of Medicine.

I would like to turn to a discussion of the basic disease process exemplified by this patient, namely, a variety of hereditary hyperlipemia resulting from deficiency of the enzyme, lipoprotein lipase. In evaluating a child with hyperlipemia, it is important to eliminate known causes such as uncontrolled diabetes, glycogen storage disease and nephrotic states; and, more rarely, myxedema, Niemann-Pick's disease and diffuse lipo-atrophy. In the absence of these conditions, the presence of hyperlipemia suggests a group of diseases usually called "essential hyperlipemia." When this syndrome is seen in childhood, the particular disease we are discussing today is the most common form; however, it is a rare condition in the spectrum of essential hyperlipemia seen in adults. The next question of importance is the type of hyperlipemia. Is it chylomicronemia or endogenous hyperlipemia?

Table 2 shows several lipoprotein fractions which can be separated by a variety of physical techniques. Chylomicrons and the very low density lipoproteins, which are the two major triglyceride-bearing lipoproteins in blood plasma, are less dense than the non-protein solvent density of plasma, namely 1.006. With ultracentrifugation of plasma at its own density, these two fractions will float to the top of the tube. The chemical composition of the abnormal lipoprotein in the present case was close to that of chylomicrons. Chylomicrons, being larger and less dense molecules than the very low density lipoproteins, tend to separate more readily as a cream layer, as was well demonstrated in this patient. Quite clearly he had predominantly a chylomicronemia. The very low density lipoproteins, which carry endogenous triglycerides, can accumulate in the plasma as a result of defective removal mechanisms or as a result of increased secretion from the liver. Whenever chylomicronemia predominates, the problem is generally that of defective removal. The normal mechanisms for clearing chylomicron triglycerides from the blood are so efficient that they can accommodate 200 to 400 gm of fat daily. When chylomicrons accumulate and persist from meal to meal, deficient removal mechanisms should be suspected.

TABLE 2.—*Lipoprotein Classes in Human Blood Plasma*

Class	*Density*	*Molecular Diameter (Ångströms)*	*Electrophoretic Mobility (starch gel)*
Chylomicrons	..~0.96	500-10,000	Variable, α to β
Very low density lipoproteins	..0.96-1.006	200-1,000	α_2 or "pre-β
Low density lipoproteins	..1.006-1.06	200	β
High density lipoproteins	..1.06-1.21	100	α_1

Patients with defective removal mechanisms will respond to restriction of dietary fat. In cases resembling the present one, reported several years ago, three of six siblings had this syndrome.[4] Neither parent had lipemia. This family lived on a farm in Maryland and ate large amounts of eggs and chicken. The childrens' plasma was lipemic when they entered the Clinical Center at the National Institutes of Health. When they were placed on a standard 1 gm per kg fat diet, (about a 70 gm fat diet for an adult), they had a very predictable triglyceride level, approximately 1,000 mg per 100 ml. When fat was eliminated from the diet, the lipemia disappeared in two to three days and single fat meals produced a very abnormal fat-tolerance curve. The effect of heparin was slight or absent in contrast to the response seen in other types of hyperlipemia. Two of the siblings in this family had had recurrent attacks of abdominal pain. When fat was restricted, all the lipoprotein lipids of density less than 1.006 fell and non-triglyceride constituents of lipoproteins accumulated in the low density lipoprotein fraction. For this reason cholesterol and phospholipid levels tend to fall less than do triglyceride levels when such patients are placed on a low fat diet.

The dramatic response to dietary fat in patients with this syndrome distinguishes it from other forms of hyperlipemia which are primarily endogenous in nature and which usually do not respond well to fat restriction. In fact, in the so-called carbohydrate-induced form, the hyperlipemia is aggravated by restriction of dietary fat. The problem we are dealing with today, then, is one of removal of chylomicrons from the blood. This process is defective in patients with this disease because of deficient removal mechanisms.

Chylomicrons are large spherical particles, approximately 3,000 Ångströms in diameter. The very low density lipoproteins containing endogenous triglycerides are about 300 Ångströms in diameter (Table 2). Their metabolism qualitatively is similar to that of chylomicrons.[5] When secretion of triglycerides from the liver is increased, as in pregnancy, a striking endogenous hyperlipemia may develop in patients with this syndrome. Chylomicrons are so large that they cannot readily pass the endothelial barrier of capillaries and there is little evidence that pinocytotic mechanisms are involved in their transport. For these reasons, much work has been devoted to the study of mechanisms by which large quantities of lipid constituents of chylomicrons can traverse the capillary wall efficiently.

One of the first hints about this mechanism was obtained when chylomicrons were collected from animals which had been fed labeled fatty acids. When such chylomicrons or endogenous lipoproteins rich in C^{14}-labeled triglycerides are injected into animals, rapid removal of the triglycerides occurs with a half-time of five to 15 minutes. A very rapid appearance of the radioactivity injected in the form of triglyceride fatty acids is seen in an unesterified form, the so-called free fatty acids which are carried in the plasma bound to albumin. There is a rapid peaking of radioactivity and then a gradual decrease in the free fatty acids, roughly parallel to the disappearance curve for the triglyceride fatty acids. This indicates that, in association with the removal process, there is a chemical reaction which results in hydrolysis of the triglycerides to yield free fatty acids.

It was shown a number of years ago by Hahn that lipemia rapidly disappears when heparin is given to a lipemic dog. We now know that this is the result of liberation of an enzyme from tissues into the blood. This lipase is called clearing-factor lipase in Great Britain, and lipoprotein lipase in this country. Lipoprotein lipase catalyzes the hydrolysis of triglycerides, either in the form of chylomicrons (exogenous triglyceride) or in the form of very low density lipoproteins (endogenous triglycerides), in order to release free fatty acids and glycerol. This reaction is thought to account for the rapid hydrolysis observed when labeled chylomicron triglycerides are given intravenously.

There is other evidence that this enzyme is responsible for the hydrolytic process. First of all, as I have mentioned, when one administers heparin, lipemia clears rapidly as the enzyme is liberated into the blood. Conversely, injection of protamine into a lipemic animal decreases the rate of removal of chylomicrons. Protamine can also induce and maintain lipemia in fasted animals and there is evidence that this occurs because of inhibition of removal mechanisms for endogenously-produced triglycerides. It is known from studies *in vitro* that protamine inhibits lipoprotein lipase. Furthermore, the ability of tissues to take up chylomicron triglyceride fatty acids from the blood correlates very closely with the activity of lipoprotein lipase in that tissue. This is shown best in the case of adipose tissue, in which lipoprotein lipase activity varies strikingly with the nutritional state. After glucose ingestion, a large amount of enzyme activity is extractable from adipose tissue in both rats and rabbits. In the fasting state, this tissue contains very little enzyme activity. If labeled triglycerides are injected into rats or rabbits which have been fed, the triglyceride fatty acids accumulate in the adipose tissue; in contrast, in the fasting animal almost none of the triglyceride fatty acids are found in the tissue. For example, when triglycerides in which palmitate has been labeled with C^{14} are injected into fasting rabbits, only 1 to 3 per cent of the radioactivity is found in the total adipose tissue after two hours. In fed rabbits, virtually half of the injected radioactivity is found in the total adipose tissue at this time. This has also been shown *in vitro*. Dr. Alyce Bezman-Tarcher, Dr. James M. Felts and I demonstrated that incubation of labeled lipoproteins with adipose tissue from fed animals led to brisk uptake. This was shown to be well correlated with the enzyme activity extractable from the same tissue. This is further cogent evidence, albeit indirect, that lipoprotein lipase is involved in the removal process.

A number of years ago on the basis of the data which I have shown you, we and others postulated that the enzyme, lipoprotein lipase, acts primarily at the level of the capillary wall. In recent electron microscopic studies, it has not been possible to demonstrate transport of intact chylomicrons across capillaries. Electron micrographs have shown chylomicrons "sticking" at the surface of capillaries in adipose tissue where we believe the enzyme lipoprotein lipase to be located. Chart 2 demonstrates in more detail our current concept of how the fatty acid constituents of triglycerides pass across capillary membranes. At the capillary surface, an enzyme-substrate complex forms, hydrolysis then occurs, and the fatty acids released either circulate in the blood, bound to albumin, or are transported by a carrier mechanism into the cell where they can be esterified to form triglycerides. In the case of other tissues such as muscle, this same reaction can occur. In these tissues the fatty acids can then be burned in the mitochondria to supply the demands of cellular metabolism.

Additional evidence which suggests that the enzyme is located at some site very close to the capillary surface is the following: If heparin is injected into the femoral artery of an animal in which the femoral vein of the same side has been cannulated, enzyme activity appears in the femoral vein blood within seconds. It is very difficult to visualize how a molecule such as heparin, with a molecular weight of about 15,000, could gain access to the cell parenchyma and release the enzyme so that it could appear in the blood in a single circulation.

ASSIMILATION OF TRIGLYCERIDE FATTY ACIDS BY ADIPOSE TISSUE

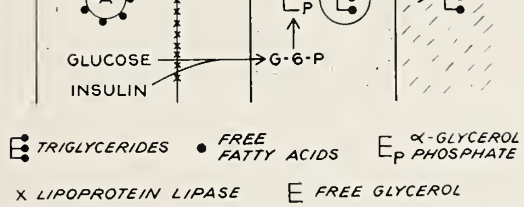


Chart 2.—Postulated mechanism for transporting and storing fatty acid constituents of plasma triglycerides in adipose tissue. This chart was obtained from *Fat as a Tissue*, edited by Rodahl and published by McGraw-Hill Company in 1964, and is reproduced with their kind permission. A = Ångströms. C = Carbon. G-6-P = Glucose-6-phosphate.

With this evidence that lipoprotein lipase may be essential for normal removal of chylomicrons, we would certainly suspect that deficiency of this enzyme could account for the type of hyperlipemia shown in the patient presented today. This has, in fact, been observed; it was first shown in the previously mentioned family that was studied at the National Institutes of Health. Assay of lipoprotein lipase activity in blood plasma is performed as follows: A standard amount of heparin is injected intravenously and samples of blood are obtained at various periods of time (usually 10 minutes) after injection. The plasma is separated and incubated under conditions conducive to optimal enzyme activity. An excess of albumin is added to accept the fatty acid liberated. A substrate, usually coconut oil emulsion, is also added in excess.[3] Coconut oil is a peculiar oil; its triglycerides contain primarily lauric acid, a C-12, saturated fatty acid. Normal chylomicron triglycerides contain predominately C-16 and C-18 fatty acids, either saturated or unsaturated. However, coconut oil triglycerides are readily hydrolyzed by lipoprotein lipase. The three affected siblings in the family previously described had very low activities of lipoprotein lipase in plasma after the injection of heparin, whereas two subjects with endogenous forms of hyperlipemia, not associated with predominant chylomicronemia, had normal enzyme activity.

To determine if the intrinsic activity of the enzyme was low in the affected siblings or whether the low activity resulted from presence of inhibitors or lack of activation in the subjects' plasma, the following studies were done. Pre-heparin and post-heparin plasma from normal subjects was mixed with plasma from subjects with hyperlipemia. Pre-heparin plasma from hyperlipemic subjects did not inhibit lipolytic activity of the post-heparin plasma from normal subjects. Enzyme activity could not be increased by adding pre-heparin plasma from normal subjects to the patient's post-heparin plasma. Thus, there appeared to be a true defect in the activity of the enzyme rather than one resulting from extraneous factors in the plasma.

To determine whether the chylomicrons of the hyperlipemic subjects were abnormal, a high fat diet was fed to one of the hyperlipemic subjects and chylomicrons were harvested from the plasma. These chylomicrons were then injected into a normal subject and a hyperlipemic sibling, who were on a low-fat diet at the time of the study. The injections were given on three separate days. On the first day, a standard amount of chylomicrons was injected; the normal subject removed them with a half-time of 17 minutes (a normal value), whereas the subject with hyperlipemia required 100 minutes to remove half of the chylomicrons from the blood. Therefore, the substrate behaved normally when exposed to normal mechanisms for removal. We were also able to increase the removal rate with heparin and decrease it by pre-treatment with protamine sulfate in the normal subject. As expected, this could not be done in the subject with presumed deficiency of the enzyme. This provided confirmatory evidence that the enzyme was not only deficient in post-heparin plasma but could not be activated normally for *in vivo* functions.

Assay of lipoprotein lipase in the patient presented today is shown in Table 3. This assay was done using an artificial emulsion containing soy bean oil, which consists primarily of C-16 and C-18 saturated and unsaturated fatty acids, as described by Boberg and Carlson.[1] Under these conditions, the nature of the triglyceride being attacked by the enzyme is similar to that contained in chylomicrons. Additionally, in contrast to the commonly used coconut oil emulsion (Ediol®), it contains no monoglycerides. Since there is evidence that more than one lipase may be present in post-heparin plasma, it is possible that the nature of the substrate affects the specificity of the assay for lipoprotein lipase. Values of lipoprotein lipase were about 25 per cent of normal in the patient presented today. Lipoprotein lipase obtained from adipose tissue is effectively and almost completely inhibited by 0.5 molar sodium chloride. When we use coconut oil emulsion as a substrate in post-heparin plasma, we obtain variable inhibition with 0.5 molar sodium chloride. Using soy bean emulsion, we obtain about 80 per cent inhibition. In the hyperlipemic subject, no inhibition of enzyme activity was produced by 0.5 molar sodium chloride. It is possible, therefore, that the small enzyme activity in the patient's plasma is not lipoprotein lipase but a separate enzyme which has activity toward soy bean oil triglycerides. This seems reasonable because it is unusual to find 25 per cent of normal enzyme activity in a homozygous state which is presumably determined by a recessively-transmitted gene.

TABLE 3.—*Lipoprotein Lipase Assay of Plasma in Present Case (Method of Boberg and Carlson)*

	Enzyme Activity (μEq per minute and per ml of plasma)	
	Normal Values	Patient
In standard buffer	∼0.2	0.05
In standard buffer +0.5 M NaCl	∼0.04	0.06
Activity inhibited by 0.5 M NaCl	∼0.16	nil

I will conclude by referring to the question of pancreatitis and hyperlipemia. We have studied three additional patients with this particular form of hyperlipemia who had clearly documented pancreatitis. In one a pancreatic pseudo-cyst developed, another had acute hemorrhagic pancreatitis with shock and tetany, and a third had diffuse pancreatic calcifications. In all cases, recurrent attacks of pancreatitis can be prevented. As first shown by Klatskin and Gordon,[8] the attacks are completely prevented by restricting dietary fat. This usually requires a diet containing about 30 gm of fat per day.* When triglyceride levels remain less than 500 to 600 mg per 100 ml, we have never seen attacks of pancreatitis in hyperlipemic subjects. In some cases, attacks of pancreatitis can be produced at will by feeding fat.

We have considered the following possible mechanisms as a result of the demonstration by several investigators that free fatty acids activate certain clotting factors and tend to produce thrombosis. This is particularly true for saturated fatty acids such as palmitic acid and stearic acid. Although it is not certain how these fatty acids interact with the clotting mechanism, there is evidence that they activate either plasma thromboplastin antecedent (PTA) or Hageman factor or possibly both. In the presence of hypertriglyceridemia, whether as chylomicronemia or as very low density hyperlipoproteinemia, large amounts of substrate are available for lipase action. Leakage of small amounts of lipase from pancreatic cells into the pancreatic capillaries could result in intense lipolysis and release of fatty acids locally which could activate the clotting mechanism and cause thrombosis. The fatty acids might also interact with calcium to form insoluble soaps. Since calcium ion is involved in the normal integrity of the capillary wall, capillary damage could result. These phenomena might lead to further release of pancreatic lipase, producing a self-intensifying process. Although there is no direct evidence for this hypothesis, it does provide an explanation for the relation between the degree of hypertriglyceridemia and the occurrence of pancreatitis. I will mention in closing that hyperlipemia can also result from pancreatitis. In those cases in which transitory hyperlipemia is associated with pancreatitis, the patient is usually a severe alcoholic. Abstaining from alcohol generally leads to subsidence of both pancreatitis and hyperlipemia.

---

*In other forms of essential hyperlipemia, other measures which reduce triglyceride levels, such as restriction of caloric intake, will prevent pancreatitis.

DR. KENNETH L. MELMON*[2]: I was fascinated by your proposal for pathogenesis of pancreatitis which stressed an important step—activation of Hageman factor. As you know, this reaction is also important in the activation of kallikrein. The latter has been implicated, either in the pathogenesis or as a result of pancreatitis. Investigations have attempted to correlate the arterial content of kallikrein and the peptides such as bradykinin with the manifestations of pancreatitis. Some groups feel that kinin release may be responsible for the flush and hypotension seen with the disease.

DR. HAVEL: As I recall, I think that Dr. Oscar Ratnoff feels that it is not Hageman factor but plasma thromboplastin antecedent (PTA) that is activated by fatty acids. But this is a point for the experts. Thank you for that suggestion.

DR. WILLIAM A. ATCHLEY*[3]: As a newcomer in this field, having been in it for about an hour or so, I wonder if heparin physically alters the enzyme which is already present in the blood?

DR. HAVEL: That was the original thought for the heparin effect. However, addition of heparin to lipemic plasma does not activate lipolysis. Heparin must circulate through a capillary bed in order to obtain a substance in the plasma which can be purified as a protein.

DR. ATCHLEY: Is there a temperature optimum?

DR. HAVEL: Yes, the temperature optimum is 37°C (98.6°F), the pH optimum is about 8.6 and it is inactivated by heat. It is absorbed, like prothrombin, on calcium phosphate gel and eluted with citrate. In this way, it can be purified substantially. It has all the qualities of an enzyme and we know that it activates the hydrolytic process. It is conceivable that another substance is released from capillaries by heparin which then activates a plasma lipase. Unfortunately, it has thus far not been possible to purify the enzyme to an extent which will allow study of its kinetic behavior.

DR. HIBBARD E. WILLIAMS*[4]: Is it possible that there is an inability of the tissue to respond to heparin?

DR. HAVEL: Lipoprotein lipase activity is regularly released from normal human adipose tissue incubated with heparin.[9] In 1962, we assayed adipose tissue from one of our subjects with abnormally low activity in post-heparin plasma and could detect none.

DR. EUGENE EISENBERG*[5]: Do you think this patient's failure to grow is secondary to the hyperlipemia or to the inability to transport fatty acids?

DR. HAVEL: I doubt that as regards energy needs of tissues, it results from the inability to transport fatty acids. The ability to mobilize fatty acids from adipose tissue and burn them elsewhere persists. Intermediary metabolism in general appears to be normal. I think it is more likely that uptake of chylomicrons in the spleen is in some way related to the growth failure. This is speculation. The patient appears to have normal pituitary function, since there are readily detectable levels of growth hormone in plasma. The slight increase in plasma growth hormone after insulin may not be a reliable indicator of growth hormone deficiency in children.[7] It will be interesting to follow the linear growth of this patient while on a fat-restricted diet.

EDITOR'S NOTE: In the seven months following discharge from hospital, during which time the patient has been maintained on a fat-restricted diet, he has grown 4 cm in height. The spleen has become much smaller. It now extends only to the level of the umbilicus, and the splenic notch is no longer palpable.

REFERENCES

1. Boberg, J., and Carlson, L. A.: Determination of heparin-induced lipoprotein lipase activity in human plasma. Clin. Chem. Acta 10, 1964, p. 420-427.

---

*[2] Assisatnt Professor of Medicine and Pharmacology, and Associate, Cardiovascular Research Institute.

*[3] Associate Professor of Medicine and Associate Research Physician, Cancer Research Institute.

*[4] Assistant Professor of Medicine.

*[5] Associate Professor of Medicine.

2. Bürger, M., and Grütz, O.: Über hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut. Archiv. für Derm. und Syph., 166:542, 1932.

3. Fredrickson, D. S., Ono, K., and Davis, L. L.: Lipolytic activity of post-heparin plasma in hyperglyceridemia. J. Lipid Res., 4:24, 1963.

4. Havel, R. J., and Gordon, R. S., Jr.: Idiopathic hyperlipemia: Metabolic studies in an affected family. J. Clin. Invest., 39:1777, 1960.

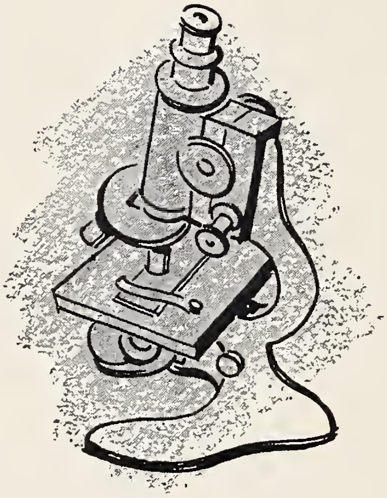
5. Havel, R. J.: Metabolism of lipids in chylomicrons and very low density lipoproteins in Handbook of Physiology (Renold, A. E. and Cahill, G. F., Jr., Eds.). Washington, D.C.: American Physiological Society, Vol. 5, 1965, p. 499.

6. Holt, L. E., Aylward, F. X., and Timbers, H. G.: Idiopathic familial hyperlipemia. Bull. Johns Hopkins Hosp., 64:279, 1939.

7. Kaplan, S. L., et al.: Serum growth hormone response to insulin-induced hypoglycemia in disorders of growth. J. Ped., 67:956, 1965.

8. Klatskin, G., and Gordon, M.: Relationship between relapsing pancreatitis and essential hyperlipemia. Amer. J. Med., 12:3, 1952.

9. Nestel, Paul J., and Havel, R. J.: Lipoprotein lipase in human adipose tissue. Proc. Soc. Exp. Biol. & Med., 109:985, 1962.



Editor
DWIGHT L. WILBUR, M.D.
•
Acting Editor
EDGAR WAYBURN, M.D.
•
Assistant to the Editor
ROBERT F. EDWARDS
For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MacLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

California
Medicine

EDITORIAL

Dr. Edgar Wayburn, long a member of the Editorial Board of California Medicine, has been appointed Acting Editor to serve during the absence of Dr. Dwight L. Wilbur on vacation. The Council of the CMA made the appointment at its meeting in September. Dr. Wilbur will return early in November.

Medicare and Medi-Cal To Date

The medicare program went into effect 1 July of this year with a minimum number of problems. Hospital benefits totaling over $23 million were paid by the two Blue Cross Plans in California for over fifty thousand admissions for July through September. Nationwide, it is estimated that hospital admissions will run about one hundred thousand a week.

California Physicians' Service and Occidental Life Insurance Company combined (two carriers in California administering Part B benefits) had received over three hundred thousand Medicare claims for physicians' services as of 30 September. Since many of the claims for physicians' services are submitted to establish a beneficiary's deductible, not all claims will necessitate a payment.

In the beginning the signatures of patients were required on all claim forms. This requirement was studied by the Social Security Administration (SSA) and revised because it was found to be cumbersome. One signature by the patient will suffice to support claims for professional services in hospitals. The requirement of a patient's signature has also caused difficulty in the handling of claims for the treatment of patients who have died. Most health insurance programs permit such claims to be honored when made by a spouse or the family, without a formal court order, and SSA is trying to work out a procedure.

The carriers report that a substantial number of claim forms have had to be returned for further information before they could be processed, but this number is rapidly declining. They further report that the most usual problems confronting the persons who process the claim are:

1. Failure to use the SSA claim Form No. 1490 for physicians' services.

2. Failure to show the suffix on the beneficiary's health insurance number (the letter or letters following the number).

3. Lack of the appropriate Relative Value Study code number.

4. Omission of the physicians' license number.

5. Working out arrangements between hospital-based specialists and hospitals on methods of payment.

Joint teams made up of SSA employees and representatives of Blue Cross and other intermediaries have been visiting hospitals in larger cities to observe admission, billing and payment procedures now in operation, with a view to improving the effectiveness of the forms and procedures used, and to keep paper work at a minimum. The Secretary of Health, Education, and Welfare has appointed an eleven-man advisory group to provide continuing consultation on ways to improve procedures, policies and relationships.

The SSA has reported that 97 per cent of the general hospital beds in the country have been approved for participation in the Medicare program. In California, 572 hospitals have signed up to participate and only 26 of those that applied did not meet the conditions of participation.

The State of California has "purchased" physicians' benefits under Medicare for eligible welfare recipients 65 and over—those on Old Age Assistance and those under the Aid to the Blind and Aid to the Totally Disabled programs. These recipients will be covered by benefits under two programs, Medicare and the California Medical Assistance Program known as "Medi-Cal." The Medi-Cal program pays the deductibles and coinsurance for these beneficiaries. CPS administers both programs. A single claim form is used for both programs—SSA form No. 1490 for physicians' services. Some initial difficulty has been encountered in determining eligibility for this group of claims.

CPS has received over fifty thousand of these combined claims. The Medi-Cal program does not permit payment to be made by the carrier to the beneficiary; hence, the acceptance of an assignment will be necessary for this welfare group in order for a physician to receive full payment.

The end of September marked the seventh complete month for the operation of the Medi-Cal program. The two Blue Cross Plans have processed over five hundred thousand claims from hospitals, nursing homes and home health agencies, and have paid over $100 million on these claims.

California Physicians' Service, during this period, received over six and a half million claims from physicians, dentists, pharmacies, nurses, podiatrists, optometrists, chiropractors and others. Over $66 million has been paid on these claims. The three largest in numbers are:

	Claims Received	*Total Amount Paid*
Physicians	1,752,000	$33,000,000
Dentists	234,000	$10,326,000
Drugs	4,061,000	$14,000,000

More than 16,500 physicians have been paid under this program.

Lack of an eligibility record remains one of the chief causes for delay in payment of claims. Automatic equipment is used for this purpose. During the early months of the program, it has been necessary to find and eliminate many technical and mechanical problems.

The State Department of Finance announced that effective 1 September 1966 the schedule of maximum allowances for laboratory services has been raised, based on a conversion factor of $5 rather than $4 on the 1964 Relative Value Studies.

Other changes are under consideration or may become necessary as conditions change or experience is gained.

The CMA has strongly urged that provision be made for direct billing of patients by physicians under this program. However, the regulations adopted do not permit CPS to reimburse recipients but only to pay vendors. Continuing efforts are being made to permit direct billing with at least the group II beneficiaries—those not receiving money aid but who need some financial help to pay for their medical care.

The President has ordered that a study be made of the rising health care costs. In view of recent developments concerning salaries of employees in California, this study will be watched with great interest.

It is reported that the House Ways and Means Committee is working on an amendment to Title XIX which would limit its benefits to families, at a set percentage—such as 20 per cent—above the welfare level. Apparently no other amendments will be seriously pressed during this session of Congress.

The surprisingly smooth functioning of the programs thus far and the willingness of the administrative officers to give careful consideration to medical and hospital management suggestions for improvements in operation and equity, bespeak a mutual respect and spirit of cooperation that augur well for necessary changes and the preservation of good medical care to the eligibles. There have been delays in paying some physicians and other providers, due in most instances to problems incident to setting up a new program. Checks now are going out with greater speed and we are assured that the backlog will be substantially reduced soon.

That a program so large has become so quickly a functioning organism is a remarkable accomplishment. The credit for it can be shared by the government personnel and the medical, hospital and insurance consultants who designed the plans and review them constantly for needed changes, by the carriers who process the claims, by the treating physicians and their office assistants who have been called upon to familiarize themselves with myriad new details, and by the representatives of the medical profession who continue to serve both Medicare and Medi-Cal in various administrative, advisory and supervisory capacities.

Editorial Comment

A Rational Basis for the Use Of Spinal Anesthesia

SPINAL ANESTHESIA has so much to recommend it pharmacologically, physiologically and clinically that the still limited use of the method and the granite prejudices against it are perplexing. In the circumstances, examination of the uses of spinal anesthesia and inquiry into the reasons for the enduring objections to it seem likely to help.

Historically, attitudes toward anesthesia by subarachnoid block have been characterized by alternating enthusiasms and rejections. Of recent years the enthusiasms of advocates of this method have been more tempered and reasonable. Meanwhile the rejections are fewer but they do not completely abate.

With anesthesia by subarachnoid block, as with almost any other procedure in the practice of medicine, success depends upon competent administration in full knowledge of the gross and subtle changes that can occur in the human organism and so demand countering changes in procedure. The anatomical changes resulting from pregnancy or obesity, for example, must be taken into account lest the level of anesthesia be inordinately high. And, for further example, the physiologic adapter responses must be borne in mind to prevent circulatory collapse.

Eversole's old dictum, "The primary contra-indication to spinal anesthesia is the absence of a spinal anesthetist," has bearing in this regard.

In most instances lack of competent ability in the administration of spinal anesthesia results from lack of training, but in a few persons it is basic. For them, anesthesiology is the wrong calling, as it is a discipline requiring technical facility.

For the most part, ineptitude in spinal anesthesia equates with unfamiliarity with detail, and in this area an anesthesiologist can improve his skills by training, observation and self-analysis. Certainly it is to be hoped that he will make the effort, for without these skills the anesthesiologist denies the patient the complete service for which he is contracting. In effect the anesthesiologist limits the exercise of his medical judgment to the use of general anesthesia. Or, if he does use spinal or block anesthesia, but only when absolutely indicated, he denies himself the chance to obtain and maintain the finesse which both he and the patient deserve. A further factor to be considered is that spinal anesthesia is a pharmacological "bargain"; the ratio of anesthesia obtained to the amount of drug used far exceeds that to be had with any other method.

Irrational prejudices—that is, those not based on inept performance—are less readily defined and consequently less susceptible of correction. Some are atavistic fears which seem to relate back as far as our quadriped days. Many patients are much more concerned about their backs than their brains. Also the attitude toward drugs applied directly to the central nervous system, as in spinal anesthesia, is considerably different than toward those applied more remotely as in inhalation or intravenous anesthesia, even though ultimately arriving at the same goal.

Some of the problem relates to a "what-I-don't-know-won't-hurt-me" attitude, while some of it comes from misconception or misapplication of imperfect knowledge. The anesthesiologist who is secure in his own knowledge and ability will use every opportunity to inform and educate and to demonstrate that irrational prejudices *are* irrational. In anesthesiology particularly we need to dissuade our patients from a common reliance upon drugs and their effects rather than upon the persons who administer the drugs and the methods by which they do it.

Selection of the method of anesthesia traditionally hinges on a review of four factors: operation, patient, surgeon and anesthetist. While Waters' dictum that the best method is the one with which the anesthesiologist is most familiar has some validity, in this day it should be expected, at least

---

Chairman's Address: Presented before the Section on Anesthesiology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 439-30th Street, Oakland 94609 (Dr. Bruce Anderson).

in California and certainly in urban hospitals in California, that the anesthetist will be an anesthesiologist in the fullest sense of the word. It should follow that he will be constantly available with all necessary knowledge and skills. Therefore the variable of professional ability should be eliminated as a factor in the selection of anesthesia.

It should be expected and accepted, however, that the variable of surgical technique and skill will affect the choice of method and agent. Unfortunately, it must also be accepted that the prejudices and preferences of the surgeon have to be considered just as are such factors as diabetes or a full stomach in the patient. But to eschew spinal anesthesia for fear of litigation on the part of either the surgeon or the anesthesiologist is professional dishonesty and a compromise of medical judgment.

Certain operations of course automatically exclude spinal anesthesia—for example, craniotomy; but others should make it a primary consideration, as for instance, cesarean section.

For a large group of patients a careful review of the factors presented may make subarachnoid block a logical choice.

The factors in the patient himself include the physiological, pathological and psychological. Fear of spinal puncture has already been considered but it should be remembered that fear of general anesthesia is just as real. Also it is well to remember the well balanced extrovert whose healthy interest in and enjoyment of the experience of an operation should not be denied.

Pathological disturbances such as coronary arteriosclerosis or coryza or anemia or ferunculosis are some of the considerations in selection of anesthetic method. Less importantly, physiologic differences such as body type or age have a bearing. From our observations of patients in the immediate postoperative period, it appears that spinal anesthesia makes the least physiological demand on the patient.

To allay the irrational fears of spinal anesthesia in the laity and overcome the prejudices against it in the medical profession which probably have come largely from witnessing or hearing of inept administration, it behooves anesthesiologists to bring their technique with this method to perfection. For while technical brilliance may not be necessary to make spinal anesthesia possible, it is required to make it acceptable, to make it presentable and even to make it enjoyable for both the anesthetist and the patient. Technique is a matter of considered detail. Careful positioning of the patient, the use of fingers rather than the whole arm when inserting the needle, the use of fine gauge needles—No. 26 or if necessary No. 24—accurate judgment of dosage and careful selection of specific drugs are all part of careful technique. Spinal anesthesia should not be thought of as a method but as a group of methods—hyperbaric, hypobaric, isobaric, unilateral, high, low, long or short—to fit the circumstances of the moment. Nor should it be thought of as something special or major but rather as a direct, efficient method of anesthesia that is as applicable to a ten-minute procedure as to one that takes five hours.

This is not to give the impression that the author treats spinal anesthesia as a single entity. The approach to anesthetic balance is the same as that used with any other method. Spinal anesthesia is used alone much of the time, sometimes with very little predemedication and sometimes with quite heavy sedation and such additional supplements as are indicated. Combinations with general anesthesia are often made deliberately, especially for operations on the bowel or in the upper abdomen. Particular attention is given to positions of comfort and to fluid intake both during the operative and immediate postoperative period. The adjuvants used include ultra-short and short acting barbiturates, phenothiazines, hypnosis and even mirrors. A patient contentedly watching his own operation is the most tranquil I know.

In my practice in a general hospital, regional anesthesia is used in about 25 per cent of cases and it is induced by subarachnoid block in approximately 60 per cent of the cases in which it is used. I believe that these should not be unusual figures and that practices which do not approach them are offering patients less than they deserve.

BRUCE M. ANDERSON, M.D.
Oakland

California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 523rd Meeting of the Council, San Francisco, Hyatt House, 30 July 1966.

The meeting was called to order by Chairman Anderson at the Hyatt House, San Francisco, on Saturday, 30 July 1966, at 9:20 a.m.

Roll Call

Present were President MacLaggan, President-Elect Morrison, Speaker Quinn, Vice-Speaker Telford, Secretary Weyrauch and Councilors Isenhour, Eastman, Melone, Todd, Gooel, Taw, Bullock, O'Connor, Ham, Rogers, Crum, Boyle, Burnett, Richard S. Wilbur, Miller, Fenlon, Kay, Kaiser, Anderson, Yant, Grunigen and Immediate Past President Teall. Absent for cause were Editor Dwight L. Wilbur and Councilors Maguire, Watts and Longmire.

A quorum present and acting.

Present by invitation were Messrs. J. Collins, Eberlein, Whelan, Blackley, Clark, Klutch, E. Collins, Edwards, Lemos, Goldman, Curley, Hetland, Doctor Miller, Mmes. Griffith and Redfern, and Misses Price and Belser of CMA staff; Mr. Hassard, legal counsel; component society executives Scheuber of Alameda-Contra Costa, Rideout of Butte-Glenn, Lingerfelt of Fresno, Dalbec of Los Angeles, Colvin of Monterey, Bannister of Orange, Walters of Riverside, Donmyer of San Bernardino, Neick of San Francisco, Wood of San Mateo, Marvin of Santa Barbara, Donovan of Santa Clara and Brown of Sonoma; Messrs. Paton, Saylor, Heller, Babb, Light and Potloff of California Physicians' Service; Messrs. Read, Putnam, Brown and Salisbury of the Public Health League; Mr. Gould of the AMA; Doctor Cullen of UC, San Francisco, School of Medicine; Doctor Tupper of UC at Davis; Fernando Torgerson, Ph.D., and Doctor Rosen, State Health and Welfare Agency; Doctor Breslow, State Department of Public Health; Doctor Lowry, State Department of Mental Hygiene; Doctor Coombs, State Board of Medical Examiners; Mrs. Bacon, Woman's Auxiliary to the CMA; Mrs. Stanley, California Nurses Association; Doctor Smith, California Dental Association; Doctors Herzog, Lindsey and others.

JAMES C. MacLAGGAN, M.D.	President
JOHN G. MORRISON, M.D.	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH W. TELFORD, M.D.	Vice-Speaker
CARL E. ANDERSON, M.D.	Chairman of the Council
ALBERT G. MILLER, M.D.	Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D.	Secretary
DWIGHT L. WILBUR, M.D.	Editor
EDGAR WAYBURN, M.D.	Acting Editor
HOWARD HASSARD	Executive Director

General Office, 693 Sutter Street, San Francisco 94102 • 776-9400
ED CLANCY . . . . Southern California Office
1515 N. Vermont Avenue, Los Angeles 90027 • 663-8071

1. *Minutes for Approval*

Minutes of the 522nd meeting of the Council, held 18 June 1966, were approved with one addition: Paragraph (e)(i) of section 51309 of CAL-MAP regulations, with proposed changes to include under the program *registered* physical therapists in private practice. The amended paragraph as adopted by the Council reads:

> "Except that, on and after 1 July 1966, wherever, within reasonable distance of the beneficiary's residence, or physical location if in a nursing home, there is a hospital, and organized hospital outpatient service, a certified home health agency, a rehabilitation center, or a recognized hearing center, *or at other facility of a person qualified in the state to provide the specific service,* such services as applicable shall be covered when provided by, under arrangements with, such facilities."

2. *Membership*

(a) On motion duly made and seconded, 169 members whose dues were delinquent and now paid, were reinstated.

(b) On motion duly made and seconded, eleven applicants were voted election to Associate Membership. These were: Ronald R. Cameron, John V. Sessums, Jr., Alameda-Contra Costa County; Barbara E. Kovats, Lester Lehman, Los Angeles County; Eugene Prout, Napa County; James S. Ray, Jr., Orange County; Joseph A. Trackman, Riverside County; Lester E. McDonald, Sacramento County; Dorothee Perloff, San Francisco County; Wm. Norman Sears, Santa Clara County; Edward T. Jewett, Sonoma County.

(c) On motion duly made and seconded, two members were voted election to Retired Membership. These were: Arthur T. Bailey, Riverside County; Herbert Larson, San Joaquin County.

(d) On motion duly made and seconded, a reduction of dues was voted for seven members for reasons of prolonged illness or postgraduate education.

3. *Report of the President*

President MacLaggan reported on several meetings he had attended since the last session of the Council. Among these was a meeting of the CMA Committee on Emergency Action with the officers of the California Hospital Association. After briefly discussing the meeting, which centered on the creation of a "Health Manpower Council," President MacLaggan moved that the CMA encourage its representatives to participate with the CHA and other interested parties in the development of a "Health Manpower Council."

ACTION: Voted to encourage CMA participation in the "Health Manpower Council" along with the California Hospital Association and other interested parties (in line with recommendations submitted by Commissions on Community Health Services and Allied Health Professions and Services). (Committee on Emergency Action to bring together appropriate group to represent CMA in this project, including the Chairmen of the Commissions on Community Health Services and Allied Health Professions).

President MacLaggan also discussed CMA representation at the meeting of the Organization of State Medical Association Presidents, scheduled for 26 and 27 August in Chicago. Doctor MacLaggan suggested that in addition to paying expenses for CMA's President and President-Elect, CMA should underwrite the attendance of CMA Past-President Teall, who is president of the national organization.

ACTION: Voted to authorize payment of expenses for Past President Teall's attendance at the Meeting of the Organization of State Medical Society Presidents, 26 to 27 August in Chicago.

4. *Committee on Committees*

Chairman Morrison offered the following two nominations on behalf of the Committee on Committees:

Appeals Committee—Thomas Elmendorf of Willows

Advisory Committee to the State Department of Education on Public School Health—Thomas Robinson of Newport Beach

ACTION: Voted approval of the above nominations.

Nominations to the Committee on Organizational Review and Planning were deferred until after the September meeting of the Council.

Chairman Morrison reported that the Committee on Committees was currently preparing recommendations to the AMA Board of Trustees regarding appointment of California physicians to AMA committees. It was suggested that a list of California doctors currently serving on AMA committees be circulated to Council members, who were encouraged to send their suggestions for appointments to Doctor Morrison.

5. *Finance Committee*

Chairman Kay reported that CMA had recently received a request from the California Heart Association that CMA pay additional monies to help cover the budget exceeded for a conference held on 3 and 4 December 1965. It was recommended that the Council deny payment of the additional money over and above the $800 contribution originally pledged by the CMA.

ACTION: Voted to deny payment of the additional monies.

6. *Ad Hoc Committee on Workmen's Compensation*

Chairman Anderson reported on recent activity relating to payment to physicians under Workmen's Compensation, drawing the attention of the Council to the detailed written report which they had received. The report summarized hearings held on 5 and 7 July by the Division of Industrial Accidents in response to a petition filed by the California Workmen's Compensation Institute and the State Compensation Insurance Fund. The petition requested a new minimum medical fee schedule based upon the format of the 1964 *Relative Value Studies* with a conversion factor of $5.00. CMA testimony opposed, in principle, a specific dollar conversion factor; however, the petition was supported, with reservations, on the basis that it represented a step in the right direction which would be acceptable for a brief interval until a "usual, customary and reasonable" charge basis could become effective, as requested by pending legislation. Doctor Anderson paid tribute to the work of Doctor Packard Thurber, Jr., and others in making possible the application of the *Relative Value Studies* to payment under the Workmen's Compensation system.

7. *Task Force on P.L. 89-97*

Chairman Teall reported on the complex problems encountered in the development of criteria for "freestanding" clinics and recommended, on behalf of the Task Force, that the Council direct the Commission on Medical Services, working with the Commission on Community Health Services and county medical societies, to make an in-depth study of "free-standing" clinics, including locations, functions, billing procedures, relations with county societies—and to report back to the Council.

ACTION: Voted to have the study on "free-standing" clinics undertaken by the Commission on Medical Services, in conjunction with the Commission on Community Health Services and county medical societies.

With regard to the Task Force's activities in response to House of Delegates Resolution 56-66 (Channeling of Funds), Doctor Teall reported that the matter had been explored at length by the Task Force at its last meeting and that an ad hoc Committee of the Task Force was appointed to attempt to develop a cohesive policy position on the county/teaching hospital situation and to report back to the Task Force, which would, in turn, report to the Council. Committee members are: Doctors Morrison (Chairman), Fenlon, Arthur Howard, Isenhour and Todd. The Task Force recommended that the Council direct the appropriate agency within CMA to conduct an immediate and continuing survey of activities in each of the 104 county/teaching hospitals in California.

ACTION: Voted to conduct immediate and continuing research on activities in county/teaching hospitals throughout the State.

The Task Force also asked that the Council reaffirm its previous position that insofar as possible, the Crippled Children Services Program be integrated into the California Medical Assistance Program (Medi-Cal).

ACTION: Voted to reaffirm above position.

House of Delegates Resolution 104-66 (Physician's Compensation for Administrative Requirements) was discussed. It was moved to adopt a position previously taken by the Task Force: Opposition to payment of appointed physician members of utilization committees for professional review. The Council was reminded, however, that reimbursement is available under Title 18, Part A of Medicare for hospital administrative personnel and others concerned with clerical and other duties.

ACTION: Voted to adopt the position opposing payment of appointed physician members of utilization committees for professional review.

Regarding House of Delegates Resolution 62-66 (Medical Diagnostic Procedures by Optometrists), the Task Force reaffirmed the position that ophthalmic tonometry is a specific medical diagnostic procedure and therefore is the practice of medicine. The Task Force recommended that the bulk of responsibility for this resolution remain with the Commission on Professional Welfare.

In concluding his report, Doctor Teall stated that the Task Force recognizes its status as an "ad hoc" rather than "standing" committee; thus, it is recommending transfer of as many responsibilities as possible to "standing" CMA commissions and committees.

8. *Commission on Community Health Services*

Chairman Kay announced that during the week of 31 October to 4 November, the American Public Health Association will hold its 94th Annual Meeting in San Francisco. One major topic scheduled for the meeting is the report of the National Commission on Community Health Services.

Doctor Kay drew the attention of the Council to the proposed Joint Fluoridation Project to be undertaken by the California Dental Association, the Southern California Dental Association and the CMA and recommended that the Council approve the project so that application can be made to the United States Public Health Service for a grant. The project was described as being designed to develop professional education in the uses of fluorides as dental preventive measures in all aspects.

ACTION: Voted to approve the proposed joint fluoridation project.

9. *Commission on Communications*

On behalf of the Commission, Chairman Todd reported on current Communications activities and submitted a series of recommendations for Council approval, with the following results:

ACTION: Voted to authorize preparation of a special "Interim Report" highlighting recent developments of interest to CMA Delegates and Alternates, to be distributed this fall.

ACTION: Voted approval of continuing production and distribution of the publication, "Medical Staff Bulletin," to hospital chiefs of staff in California, changing its frequency from bi-monthly to monthly.

ACTION: Voted to authorize use (within present budget limitations) of communications research in the development of a more sophisticated medical public relations effort (major projects to be approved by both Commission and Council).

ACTION: Voted approval to publicize and urge wider use of the AMA publication, "Today's Health Guide," through regular CMA channels (House of Delegates Resolution 6-66).

ACTION: Voted to approve utilization of regularly distributed CMA publications to reinforce among California physicians the important role they play in controlling venereal disease (House of Delegates Resolution 13-66).

ACTION: Voted to approve CMA's assuming an independent "medical" position on abortions, welcoming support from others, but not compromising CMA's position with those of other groups (House of Delegates Resolution 43-66).

ACTION: Voted to defer the recommendation that CMA utilize public opinion research to determine where emphasis should be placed in efforts to modify the existing State abortion law—until the next meeting of the Council, following the report by the Committee on Legislation.

ACTION: Voted to authorize the Commission to send two of its members to the AMA Public Relations Institute, 25 to 26 August in Chicago.

10. *University of California Medical Center, San Francisco*

Dean Cullen reported to the Council that Doctor Robert Fishman had been appointed as the new Chairman of the Department of Neurology at UC. Doctor Fishman comes to the UC Medical Center from Presbyterian Hospital in New York City.

11. *Stanford University School of Medicine*

A representative for Dean Glaser expressed the appreciation of Stanford to the Los Angeles County Medical Association for a scholarship made available to first year medical students.

12. *University of California School of Medicine, Davis*

Dean Tupper announced to the Council that several new faculty appointments had been made, and that as of 1 September, the following physicians would be on the faculty at Davis:

Loren Carlson, M.D., currently Chairman of Physiology and Biophysics at the University of Kentucky, will be Chief of the Division of Sciences Basic to Medicine, Chairman of Physiology and Assistant Dean of the School of Medicine at Davis.

Robert Bolt, M.D., currently Professor of Internal Medicine at the University of Michigan, will serve as Chief of the Division of Medicine, and Chairman of the Department of Internal Medicine.

Robert Hunter, M.D., currently in the anatomy department at Stanford, will serve as Professor of Anatomy at Davis.

Dean Tupper also introduced to the Council Earl F. Wolfman, Jr., M.D., who is Associate Dean of the Medical School at Davis, as well as Chief of the Division of Surgery and Chairman of the Department of General Surgery.

13. *State Health and Welfare Agency*

Fernando Torgerson, Ph.D., announced to the Council that the informal title of the California Medical Assistance Program had been changed to Medi-Cal. He also mentioned the delay encountered in claims payment due to establishing eligibility files for recipients under Medi-Cal, and said that the Agency hoped to develop a central eligibility bank by the end of August to expedite claims information to the carriers.

14. *State Department of Public Health*

Doctor Lester Breslow, director, reported to the Council that there were 78 home health agencies certified to participate under Title 18 of Medicare. He stated that this covered over 95 per cent of the population of the state, geographically, and that these were now being licensed in accordance with State law. He also said that a training program for home health aides was under way.

Doctor Breslow said that 574 hospitals had been recommended for certification under Title 18, and of these, 567 had signed agreements to participate in the program. The certification of radiological facilities and clinical laboratories is still proceeding.

Doctor Breslow also reported on the progress being made with regard to alcoholism treatment and said that under the McAteer Act, local programs would receive supporting funds.

15. *State Department of Mental Hygiene*

Doctor James Lowry, director, advised that the Legislature had provided the Department with funds for establishing a hospital for research and training with regard to the mentally retarded. He said that it was hoped that this hospital would be integrated with the new campus of the California College of Medicine (U.C.). Doctor Lowry reported that the number of persons in hospitals for the mentally ill had decreased by 3,500 in the past year. He said that the number of admissions was about the same as the previous year, but that the length of stay had been reduced in many instances.

16. *California Physicians' Service*

Doctor Richard S. Wilbur, chairman of the Board of Trustees, introduced the new president of CPS, Mr. Thomas C. Paton, who was previously president of the Minnesota Blue Shield Plan, and expressed deep appreciation to Mr. R. S. (Rusty) Saylor, who was acting president during the initiation of the Medi-Cal program.

17. *California Nurses' Association*

Mrs. Mary Stanley, president of the Association, and its executive director, Mrs. A. Lionne Conta, discussed at length with the Council the current dispute on compensation of nurses. Members of the Council concurred that one of the more important requirements for the continuing provision of optimal medical care for all Californians is an adequate level of compensation to all members of the health care team, including the nursing profession. After some discussion, the following amended policy statement was adopted:

"1. The primary goal of physicians, nurses and other members of the health care team must continue to be the provision of high quality medical care to all citizens of the state.

"2. Members of this health care team should receive reasonable and adequate compensation for their services. Determinable criteria should include the level of education and training, experience, and the degree of responsibility assumed by the respective personnel.

"3. In the interest of both patients and the public, methods should be sought to achieve these goals in a professional manner, within the framework of the voluntary democratic process.

"4. The California Medical Association will continue to cooperate with the hospitals of California and with professional organizations representing members of the health care team, for the purpose of improving the quality and increasing the availability of health manpower personnel through: (a) Improving recruitment techniques; (b) providing more educational and training opportunities; and (c) fostering adequate compensation of personnel in terms of their education, experience and degree of responsibility in health care."

18. *Woman's Auxiliary to the CMA*

Mrs. Dorothy Bacon, president of the Woman's Auxiliary, briefly commented on current activities of the organization, with particular reference to planning for the Fall Conference and Health Careers projects.

19. *AMA Delegation*

Chairman Burt L. Davis reported on highlights of the 115th Annual Convention of the AMA in Chicago. He stated that of the 21 resolutions presented by the California Delegation, about 50 per cent were approved and an additional 25 per cent were given favorable action. Doctor Davis commented that the Delegation was greatly assisted in its deliberations by having had the opportunity to meet with the Council shortly before the Convention and that the Delegation desires to hold another such joint meeting in October. There was also discussion on the desirability of non-Delegate members of CMA attending the AMA conventions.

20. *Contribution to LACMA Library*

Chairman Anderson reported that CMA had recently received a letter from Mr. John M. Connor, librarian for the Los Angeles County Medical Association, expressing sincere thanks for the continued support of the CMA and specifically, for a check recently received.

21. *Committee on Legislation*

In the absence of Chairman Kilroy, the report was presented by Mr. Ben Read, who commented briefly on the session of the Legislature which ended 7 July—the second longest session in history. He pointed out that the CMA-supported bill dealing with implied consent for blood tests of suspected drunken drivers had been signed into law. A preview of interim committee hearings on a variety of subjects was given. House Speaker Quinn commented on the drug hearings currently being held.

22. *Commission on Hospital Affairs*

Councilor Telford presented, on behalf of the Commission, four recommendations relating to health facilities planning, with the following results:

ACTION: Voted to develop and establish a set of guidelines for areawide planning of health facilities and services (to include factors of quality of care).

ACTION: Voted to develop a brochure to increase understanding of, and interest in, health facilities planning, to be publicized and distributed to CMA members and others.

ACTION: Voted to cooperate with the California Hospital Association in organizing physician-hospital administrator teams to stimulate and assist local areas with health facilities planning.

ACTION: Voted that the "Little CHIPS" program should return to its original intent, completing its first phase, then reporting back to the Council before additional activity is undertaken.

23. *Direct Billing Under Title 19*

The Council reviewed a letter from Doctor George C. Andersen, president of the Los Angeles County Medical Association, requesting that CMA clarify its policy on direct billing to reflect the AMA position, with particular reference to the 1 July 1966, CPS "Physicians' Newsletter." Doctor Richard Wilbur, chairman of the CPS Board of Trustees, explained that the CPS publication was written to be in accordance with the regulations (which, unlike the law, have no provision for direct billing) and was not a policy-making step, but merely an informational piece to clarify the actual situation. He also said that CPS had tried to simplify the billing under the two programs by coming out with a single billing form that could be used for both Title 18 and Title 19 patients, but this was in no way an effort to influence physicians to take assignments for their Title 18 patients. After some discussion, Chairman Anderson was asked to appoint an ad hoc committee to explore various facets of billing methods, payment practices by the carrier, legal interpretations and regulatory rulings as a basis for recommendations to the Council.

ACTION: Voted to direct the Chairman of the Council to appoint a committee to look into the problem of direct billing under Title 19 to attempt to clarify previous misinformation on the subject and to report back to the Council with recommendations.

In response to this action, Chairman Anderson named the following Councilors to the ad hoc Committee: Doctors Telford (chairman), Boyle, Burnett, Eastman, Miller and Richard Wilbur.

24. *Malpractice Insurance Programs*

A letter presenting a request from the Los Angeles County Medical Association that the Council give prompt consideration to problems concerning malpractice insurance programs was reviewed. The letter centered on the increasing difficulty many physicians are encountering in acquiring limits of insurance at reasonable rates.

ACTION: Voted to refer the malpractice insurance problem to the Commission on Professional Welfare, with direction to begin immediate study and to report back to the Council with recommendations.

25. *Staff Report*

Mr. Howard Hassard asked Mr. Frank Clark and Mr. William Whelan to introduce the three new CMA staff members: Mr. Edward Collins, news coordinator, working out of the San Francisco CMA office; Mr. John Curley, field services coordinator, based in the Los Angeles CMA office; and Mr. Richard Lemos, who is working out of the Sacramento CMA office in the field of governmental relations.

26. *Adjournment*

There being no further business to come before it, the meeting was adjourned at 4:50 p.m.

Carl E. Anderson, M.D., *Chairman*
Helen B. Weyrauch, M.D., *Secretary*

In Memoriam

Albert, Walter, Los Angeles. Died 29 August 1966, in Los Angeles, aged 83, of congestive heart failure. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1907. Licensed in California in 1907. Doctor Albert was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Ball, Howard A., San Diego. Died 24 August 1966, in El Cajon, aged 61, of heart disease. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1928. Licensed in California in 1928. Doctor Ball was a member of the San Diego County Medical Society.

✣

Baxter, Frank Stanley, Oakland. Died 22 August 1966, aged 79. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1914. Licensed in California in 1914. Doctor Baxter was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Chiapella, Joseph Octave, Chico. Died 20 April 1966, in Chico, aged 86, of chronic brain syndrome associated with cerebral arteriosclerosis. Graduate of the University of Southern California School of Medicine, Los Angeles, 1905. Licensed in California in 1906. Doctor Chiapella was a member of the Butte-Glenn Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.

✣

Chole, Arthur Steven, Encino. Died 23 August 1966, in Los Angeles, aged 47, of coronary artery disease. Graduate of the University of Wisconsin Medical School, Madison, 1945. Licensed in California in 1946. Doctor Chole was a member of the Los Angeles County Medical Association.

✣

Dykes, H. Robert, Sr., Santa Monica. Died 23 August 1966, in Taft, aged 76. Graduate of the Medical College of Alabama, Birmingham, 1917. Licensed in California in 1923. Doctor Dykes was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Eberhardt, Gustav, Gonzales. Died 22 June 1966, in Gonzales, aged 64, of heart disease. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Eberhardt was a member of the Montery County Medical Society.

✣

Hurwitz, Samuel Haymann, San Francisco. Died 31 August 1966, in Monterey, aged 80. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1912. Licensed in California in 1916. Doctor Hurwitz was a member of the San Francisco Medical Society.

✣

Jones, Dwight Harold, Bakersfield. Died 7 August 1966, in Bakersfield, aged 48. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. M.D. degree from California College of Medicine, 1962. Doctor Jones was a member of the Kern County Medical Society.

✣

Kibler, Robert Scott, San Bernardino. Died 6 July 1966, in San Bernardino, aged 49, of cerebral vascular accident. Graduate of the University of Colorado School of Medicine, Denver, 1941. Licensed in California in 1953. Doctor Kibler was a member of the Los Angeles County Medical Association.

✣

Lee, Charles F., Jr., Palo Alto. Died 30 July 1966, at Calvin Crest, near Yosemite, aged 43, of heart disease. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1946. Licensed in California in 1947. Doctor Lee was a member of the Santa Clara County Medical Society.

✣

Markolf, Harry Foster, Pasadena. Died 28 August 1966, in Pasadena, aged 85, of ventricular fibrillation. Graduate of Harvard Medical School, Boston, Massachusetts, 1908. Licensed in California in 1910. Doctor Markolf was a member of the Los Angeles County Medical Association.

O'CONNOR, VINCENT D., Carmel Valley. Died 4 September 1966, in Carmel Valley, aged 67. Graduate of St. Louis University School of Medicine, Missouri, 1926. Licensed in California in 1927. Doctor O'Connor was a member of the Monterey County Medical Society.

◆

O'NEIL, FRANCIS H., Eureka. Died 25 July 1966, in Eureka, aged 62, of heart disease. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1930. Licensed in California in 1931. Doctor O'Neil was a member of the Humboldt-Del Norte County Medical Society.

◆

POLEY, CYRUS WATT, El Sereno. Died 9 August 1966, in El Sereno, aged 79, of cerebral hemorrhage. Graduate of the University of Colorado School of Medicine, Denver, 1911. Licensed in California in 1921. Doctor Poley was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

ROBERTS, GORDON WILLIAM, Oakland. Died 2 September 1966, in Oakland, aged 74. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1916. Licensed in California in 1922. Doctor Roberts was a member of the Alameda-Contra Costa Medical Association.

◆

SAND, CHARLES A., San Diego. Died 28 August 1966, in San Diego, aged 53. Graduate of Cornell University Medical College, New York City, 1939. Licensed in California in 1946. Doctor Sand was a member of the San Diego County Medical Society.

◆

SHAH, AURANG, Sacramento. Died 26 August 1966, in Sacramento, aged 70. Graduate of Tufts College Medical School, Boston, Massachusetts; 1934. Licensed in California in 1938. Doctor Shah was a member of the Sacramento County Medical Society.

◆

SHARPSTEEN, JAY RANDOLPH, Oakland. Died 16 August 1966, in Oakland, aged 73. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1921. Licensed in California in 1921. Doctor Sharpsteen was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

POISON INFORMATION CENTERS

The location and telephone numbers (with area code in parentheses) of the seven official Poison Information Centers in California are listed below:

Fresno

Fresno Community Hospital (209) 233-0911; Night 233-7547

Los Angeles

Children's Hospital of Los Angeles (213) 664-2121

Oakland

Children's Hospital of the East Bay, Oakland (415) 652-5600
Alameda-Contra Costa Medical Association, Oakland (415) 652-8171

Orange

Orange County General Hospital, Orange (714) 633-9393, Ext. 273

San Francisco

Children's Hospital, San Francisco (415) 221-1200

San Jose

Santa Clara County Hospital, San Jose (408) 293-0262, Ext. 318 or 319; or 292-3141

Plan to Attend

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS PLUS THREE GENERAL MEETINGS ON THE SUBJECT:

ADVANCES IN DIAGNOSTIC TECHNIQUE

Capability • Reliability • Integration

FINAL CALL FOR
- *Scientific Papers*
- *Medical Motion Pictures*
- *Scientific Exhibits*

★ **If you have a paper** you'd like to present to your colleagues during their section meeting . . . write today to your section secretary (names and addresses of scientific section officers may be found on page 6, Advertising Section of *California Medicine*). Presentations are not limited to Advances in Diagnostic Technique.

★ **If you have a motion picture or exhibit** . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

PLANS FOR THE 1967 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

application for HOTEL ACCOMMODATIONS

NINETY-SIXTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • APRIL 16-19, 1967

BILTMORE HOTEL, LOS ANGELES

House of Delegates Opening Session Saturday evening, April 15; Scientific Programs begin Sunday morning, April 16.

1. Fill in the form below **completely** for room accommodations at the CMA's 1967 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, 693 Sutter Street, San Francisco, California 94102.
4. **DEADLINE** for housing: April 1, 1967.

HOTEL ROOM RATES*

	Single	Double and Twins	Suites
BILTMORE HOTEL			
515 So. Olive Street	10.50-17.50	15.50-21.50	30.00-55.00
MAYFLOWER HOTEL			Triples
535 So. Grand Avenue	8.50-13.50	12.00-17.50	22.00
STATLER-HILTON			Suites
930 Wilshire Boulevard	11.00-17.50	16.00-22.50	30.00-65.00

*Rates subject to change

Send to: CALIFORNIA MEDICAL ASSOCIATION—*Housing Bureau*
693 Sutter Street, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1967 Annual Session in Los Angeles, April 16-19, 1967. The first meeting of the House of Delegates begins Saturday evening, April 16; Scientific Programs begin April 16.

Single Bedroom $........ Twin-Bedded Room $........ Double Bedroom $........

Small Suite $........ Large Suite $........ Other $........

First Choice Hotel........ Second........

Arrival (date) .... Hours........ a.m. p.m. Departure (date) .... Hour........ a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of both persons for each twin-bedded or double room, and names and addresses of all other persons for whom you are requesting reservations.

—PLEASE PRINT—

Your Name .... Officer? .... Delegate? .... Alternate? .... Speaker? ....

Address .... County ....

City and State........ Zip No. ....

PUBLIC HEALTH REPORT

LESTER BRESLOW, M.D.
Director of Public Health

Problems of Aging

For a number of years emphasis has been given to the problems of aging, particularly health aspects of aging. As a result of this interest, the State Department of Public Health in 1959 published *California's Older People, Their Health Problems.*

This report presented basic data on California's older population and on causes of mortality and morbidity. It further provided information on their special health problems and on efforts directed toward solution of those problems.

Six years later, the department felt it important to again assess the health needs of the aging. This assessment, recently published as a supplement to the 1959 report, reviews current population, mortality and morbidity data, as well as events occurring since the original study that have had a significant influence on the health status of persons in this category.

There has been heartening progress in services for California's older citizens since 1959, but important gaps in health care for these persons still exist.

Since 1959, the Community Health Services and Facilities Act of 1961 and the Kerr-Mills Bill of 1962 have had significant influence on the health care of the elderly.

The Health Services and Facilities Act made federal money available for research or demonstration of out-of-hospital service to the chronically ill and aged, and Kerr-Mills provided funds for medical and hospital care for selected groups.

Nineteen new home nursing services have been established in local health departments since early in 1962; 10 local health departments and three hospitals or clinics have organized screening programs for the detection of various chronic diseases; coordinated home care programs have been established in the San Francisco and Los Angeles areas; the number of licensed nursing home and convalescent hospital beds has more than doubled since 1960, and there are now 23 approved rehabilitation centers for care of the severely handicapped.

More services must be developed before optimum medical care for the chronically ill and aged becomes a fact. And with the advent of Medicare, it is particularly important to look at the health needs of older Californians and the health services available to them at this time.

The supplemental report discloses that many elderly persons receive no medical care or reach states of extreme emergency before treatment. By no means is this always because care is unavailable; too often, social and psychological problems prevent these sick persons from seeking or accepting help.

To the aging, problems of living become increasingly complex and social problems are more intimately involved with health problems. To assist in health problems without finding help for social problems is futile. The physician alone cannot cope with these complexities; even with his customary paramedical allies he cannot manage. Needed is an increased number of social workers attracted into the health field as active participants on medical teams.

The number of general hospital beds for long-term patients in the state as a whole is perhaps adequate. However, services within these facilities are far from adequate.

Rehabilitation facilities for older persons with no work potential are far too few. Restoration or partial restoration of independence in living at any age can be as important to our economy as restoration of handicapped workers to the work force. Not only do such persons need less care from others, but their illness may be shortened and recurrence made less frequent.

As a state, as well as a nation, we have long provided extensive preventive services for infants and young children—services which make it possible to prevent certain diseases and to detect others in the incipient or early stage. These services place the child in the hands of a physician when he has the best chance to prevent or minimize illness.

Comparable services for the equally vulnerable older adults have not been developed. A yearly physical examination for every person is impossible—our supply of physicians is too inadequate —nor is there evidence that it would be helpful enough to warrant the effort; but screening for certain specific chronic diseases is possible and worthwhile.

Accidents are responsible for much disability in the age group over 65 and are among the 10 leading causes of death in each age group over 65. The greatest number of accidents occurs at home. To reduce them we need an intensive educational program geared not only toward the elderly but toward those who care for them. Housing with built-in safety features does help. Although such features are of particular importance to older persons, incorporation of them into all dwellings will help reduce the overall accident rate.

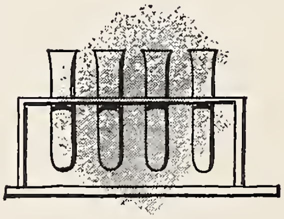
These health care needs become even more significant in light of the estimate that by 1970 the number of persons 65 years of age and over will reach nearly two million.

Mortality data in the report show heart disease, "stroke" and cancer are the leading causes of death in older age groups. In the last decade mortality rates from cirrhosis of the liver, emphysema, suicide and diabetes mellitus have increased in many of the older age groups. Causes of these increases should be investigated.

Comparison of leading causes of death by age and sex indicates that certain diseases are becoming relatively more important in the mortality picture and therefore should be given more attention. In addition to those previously mentioned, are ulcer of the stomach and duodenum and other diseases of the circulatory system which include general arteriosclerosis, gangrene, phlebitis, pulmonary embolism and infarction.

Mortality data do not indicate the prevalence of many diseases which cause morbidity in older people. Such causes are arthritis and rheumatism, diabetes mellitus, mental illness and some kidney diseases which may be present at death but are not considered as underlying causes of death and may not even be mentioned on death certificates.

All sources of morbidity information including hospital, nursing home and home care programs need to be tapped in order to obtain much needed data on causes of illness and disability among older Californians.



WOMAN'S AUXILIARY

to the California Medical Association

International Health Activities

Doctor, STOP throwing away those sample drugs, current medical journals and used instruments. Please have your aide call your county Auxiliary president for the name of the county International Health Activities chairman. These things are desperately needed in all areas of the world. REMEMBER—your discard could help a colleague somewhere in the world save a life.

Last year through International Health Activities, (IHA) members of the Woman's Auxiliary to the California Medical Association collected more than 52,000 pounds of drugs and other supplies for shipment to needy areas. About half of these went to Direct Relief Foundation, the remainder to Haiti, Mexico, South Vietnam and Hong Kong. In addition 96 journals were sent to physicians in underprivileged areas and 67 medical books, mostly PDR's were sent to mission hospitals. Three of our county Auxiliaries participated in aid to Project Hope and eight in International Hospitality efforts.

IHA is an exciting, stimulating and most worthwhile project. The diversity of this project makes it possible for each member to participate to the scope and extent that her time permits and her inclination directs.

Some of the kinds of work are as follows:

A. Distribution of medical samples either through: Direct Relief Foundation, 27 E. Canon Perdido St., Santa Barbara, California, or directly—"people to people," as is being done now by many of the county auxiliaries.

B. Distribution of Medical and Surgical supplies. (Surgical instruments; orthopedic equipment, such as artificial limbs, braces, etc.) through: Catholic Medical Mission Board, Rev. Edward F. X. Kennedy, S.J., Director, 10 W. 17th St., New York, N.Y. Direct Relief Foundation (address above).

C. Medical Journal AMA Doctor-to-Doctor Program through: Ada Chree Reid, M.D., c/o World Medical Association, 10 Columbus Circle, New York 19, N.Y. Dr. Reid will, upon request, match your gift journals with requests from your overseas colleagues.

D. Distribution of medical textbooks (not more than four years old) through: Catholic Medical Mission Board (address above); Christian Medical Council for Overseas Work, Frederick G. Scovel, M.D., 475 Riverside Drive, New York 27, N.Y.; Darien Book Aid Plan, 1926 Post Rd., Darien, Conn.; Medical Assistance Programs, Inc. (address below).

E. Medical Assistance Programs, Inc. (MAP) of the Christian Medical Society, Mr. J. Raymond Knighton, 110 N. 2nd St., West Dundee, Ill.

1. A short term missionary program sends physicians, dentists, and medical and

dental students to areas of need for short periods.

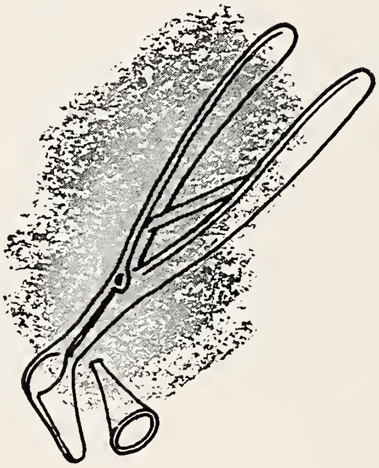
2. Provides worldwide medical relief through materiel support.

F. Project "HOPE" (Health Opportunities for People Everywhere), William B. Walsh, M.D., president, 2233 Wisconsin Ave., N.W., Washington, D.C. 20007. Project HOPE brings the skills and techniques developed by the American medical, dental and paramedical professions to the people of other nations in their own environments, adapted specifically to their needs and their way of life. (Beneficiaries: Asia, South America and Africa.) A Project HOPE program is available, at no cost, to any group or organization making a request.

G. Bandages—Bandages are needed—urgently. Both *knitted bandages* and *bandages torn from old sheets*. There is also need for *"Johnny coats"*—hospital gowns made from men's old shirts. Directions for these will be sent by this chairman upon request.

Please Doctor, clip these addresses and encourage your wife to share with you in this necessary and worthwhile project of your Medical Auxiliary. She can answer the plea of Mrs. Samuel Bacon, president of the Woman's Auxiliary to the California Medical Association: "MAGNIFY YOUR CALLING, M.D.'S WIFE!"

MRS. DANIEL J. ROTHENBERGER,
Chairman
International Health Activities
227 Prospect Drive
Redlands, California 92373



INFORMATION

The Law and Sterilization

We have received numerous requests for advice concerning sterilization procedures on both male and female patients. An understanding of the present legal basis for these procedures is helpful.

In California, there are two code provisions specifically relating to sterilization, Section 6624 of the Welfare and Institutions Code and Section 645 of the Penal Code. Section 6624 of the Welfare and Institutions Code permits the State Department of Mental Hygiene to cause sterilization of any person who has been lawfully committed or admitted to a state hospital or home, based on inheritable mental diseases, mental deficiency, or marked departures from normal mentality. Section 645 of the Penal Code provides for the sterilization of any person adjudged guilty of carnal abuse of a female under ten years of age. The procedure in such cases is authorized by the state according to eugenic sterilization statutes which must be strictly observed.

In California, there is no statute expressly granting or denying the right to perform or have performed a sterilization operation outside of state institutions. However, in line with the general consensus of opinion, the California courts would most likely hold that an operation to produce sterility when necessary for therapeutic reasons, may lawfully be performed, provided, of course, a proper consent is obtained. A California case (Danielson v. Roche, 109 Cal. App. 2d 832) which involved the removal of diseased Fallopian tubes in connection with the performance of an appendectomy, indicates that our courts recognize the legality of performing a sterilization operation for therapeutic purposes. The case of Kritzer v. Citron, 101 Cal. App. 2d 33, is to the same effect.

It would be reasonable to conclude that if a physician should become involved in a legal action arising out of an operation for sterilization of a woman, the California courts would look with favor upon the performance of the procedure, provided it was performed on solid medical grounds. As to the exact therapeutic indications that must be present to justify a sterilization operation, guideposts cannot be given, except that any physical condition which would endanger the wife's chances of surviving childbirth is undoubtedly sufficient grounds for the operation. However, as a protection to himself, consultation and approval with one or more other physicians should be obtained.

It is, of course, important to obtain the consent of the husband and wife for the performance of a sterilization operation based upon solid medical grounds. In this respect care must be taken to advise the patient that these procedures are not always successful and to avoid any language which may imply a guarantee of success. Along this line the validity of a consent to an operation that is not required for any therapeutic reason is doubtful. Further, in California, the performance of a salpingectomy or vasectomy without therapeutic indication could constitute the crime of mayhem. Until the law is settled, it is our opinion that a physician should not perform a sterilization operation except when it is therapeutically indicated or in accordance with a statute.

Specifically, economic necessities and the mental condition of the patient would not, under the present status of the law, support the performance of a sterilization procedure. The performance of surgery for sterilization under such circumstances, in my opinion, could subject the physicians involved to either civil or criminal liability or both. However, I have not found any cases instituted against physicians charging mayhem for the performance of a sterilization operation.

Peart, Baraty & Hassard
Legal Counsel to the
California Medical Association

NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

A three-day course in **the techniques of rehabilitation** care of patients is being offered to physicians 10 to 12 November at Fairmont Hospital, San Leandro. The course, largely clinical, will present details of management of adult patients requiring the application of rehabilitation techniques.

For further information and application forms, address John D. Blair, M.D., Training Program Director, Fairmont Rehabilitation Training Program, 15400 Foothill Blvd., San Leandro. Phone: 415 351-8000. Extension 441.

LOS ANGELES

Twenty-two young men and women from Los Angeles County are attending medical schools in California this fall as recipients of **Freshman Year Tuition Scholarships** awarded by the LACMA Foundation for Medical Education. Scholastic excellence, personal merit and financial need are considerations in the selection of students for the awards. Applications were accepted on the recommendation of the admissions committee and the dean's offices of the medical schools, according to Dr. Joseph P. O'Connor, president of the Foundation.

* * *

Two interprofessional conferences for physicians and clergymen will be presented in November by the University of California Extension and the UCLA School of Medicine. On 14 to 17 November the second annual UCLA Conference on Medicine and Religion will be held at the Residential Conference Center at Lake Arrowhead. The program, which is arranged in cooperation with the CMA Committee on Medicine and Religion, will focus on moral and health issues such as the prolongation of dying, the revolution in sexual morality, psychedelic drugs and social criteria for contraception. A second conference will be presented 13 November at the Glendale Adventist Hospital to consider such topics as "The Minister and the Doctor Meet at the Bedside" and "Medicine and Religion and Moral Change."

Information regarding both conferences may be obtained by contacting Dr. Donald Brayton, assistant dean, postgraduate medical education, West Medical Campus, University of California, Los Angeles.

* * *

The nineteenth annual **Midwinter Radiological Conference,** sponsored by the Los Angeles Radiological Society, will be held at the International Hotel (adjacent Los Angeles International Airport), Los Angeles, 28 to 29 January 1967.

The program will include the following speakers: Dr. G. J. D'Angio, director of radiation therapy, University of Minnesota; Dr. Benjamin Felson, University of Cincinnati; Dr. Herbert J. Kaufmann, Basler Kinderspital, Basel; Dr. John W. Laws, Radiodiagnostic Hospital, Hammersmith Hospital, London; and Dr. Richard Lester, professor of radiology, Duke University, Durham.

SAN DIEGO

The American College of Surgeons will hold the first of three 1967 Sectional Meetings in San Diego, 23 to 25 January. This is the first ACS meeting in San Diego since 1925. Headquarters will be the Hotel Del Coronado. Under the chairmanship of Dr. Maurice J. Brown, the local advisory program committee has planned a series of panels, "How-I-Do-It" clinics, symposia, scientific papers, and films designed to inform the medical profession at large about developments in surgery. The programs are open to all doctors of medicine.

* * *

Dr. Marshall J. Orloff, chief of surgery at Harbor General Hospital in Torrance since 1961, has been named chairman of the department of surgery at the **University of California, San Diego,** School of Medicine. Dr. Orloff will assume his duties next January.

SAN FRANCISCO

The 19th Annual Meeting of the **American Academy of Occupational Medicine** will be held in San Francisco, 8 to 10 February 1967.

GENERAL

A scientific program especially designed for the physician in practice is scheduled for the 20th Clinical Convention of the **American Medical Association** to be held 27 to 30 November at Las Vegas, Nevada. The four-day meeting will include scientific sessions on 18 major topics, three postgraduate courses, breakfast roundtable conferences, closed-circuit television and medical motion picture programs, and a variety of scientific exhibits.

The AMA expects special interest in the **postgraduate courses,** which have been expanded to three topics: Obstetrics and Gynecology, Fluid and Electrolyte Balance, and Cardiovascular Disease. Each course will consist of three half-day sessions, each of which will feature several outstanding teachers. There will be a $10 registration fee for each.

The topics of four **breakfast roundtable conferences** are: "An Agonizing Reappraisal of Cancer Chemotherapy," "The Problem and Potential of LSD," "The Management of Metabolic Bone Disease," and "Indication for Cardioversion."

An outstanding program of closed-circuit color television and more than 25 medical motion pictures will be presented.

Topics at the scientific sessions include: scintillation scanning, radiation and cancer, clinical pulmonary physiology, gastroenterology, futuristic diagnostic and therapeutic tools, neck pain, antibiotics, urology, aerospace medicine, unconsciousness, dermatology, juvenile diabetes, endocrine and metabolic diseases, pediatrics, surgery, hematology, psychiatry, and otolaryngology.

For advance registration at the Clinical Convention, write to the Circulation and Records Department, American Medical Association, 535 N. Dearborn St., Chicago, Illinois 60610.

For information on hotel reservations, write to the AMA Housing Bureau, Las Vegas Convention Bureau, Convention Center, Paradise Road, Las Vegas, Nevada.

The Physician's BOOKSHELF

PSYCHOPATHOLOGY OF SCHIZOPHRENIA—The Proceedings of the Fifty-Fourth Annual Meeting of the American Psychopathological Association, Held in New York City, February 1964—Edited by Paul M. Hoch, M.D., Department of Mental Hygiene, State of New York; College of Physicians and Surgeons, Columbia University, New York City; and Joseph Zubin, Ph.D., Department of Mental Hygiene, State of New York; Department of Psychology, Columbia University, New York City.

The title of this book is somewhat misleading. It is not a textbook on schizophrenia. Rather, it is a collection of papers, presented at a meeting of the American Psychopathological Association. The papers possess varying degrees of readability and pertinence. Interest in the book would be restricted to psychiatrists who have a specific clinical or research interest in schizophrenia.

The book is nicely divided into six sections. They are entitled: Phenomenology and Clinical Aspects, Psychology, Neurochemistry and Genetics, Clinical Research, Therapy and Diagnosis, Classification and Prognosis. Within each part there are four or five papers which may or may not cover the subject.

The section on phenomenology is perhaps the best and would certainly be the most interesting to a practicing psychiatrist. It starts with a history of schizophrenia by Lewis. In a very few pages Dr. Lewis outlines most of the circumstances important to an understanding of the historical evolution of schizophrenia. The discussion of Bleuler's group of symptoms and Lewis' catagorization on the types of schizophrenia is worthy of attention.

In the paper that follows, Cattell outlines the criteria for diagnosis of pseudoneurotic schizophrenia. He feels the diagnosis of this significant disorder is made too infrequently. The paper ends with an instructive and readable case history.

The third article is by Arieti on the subject of schizophrenic cognition. Arieti feels cognitive alterations are an important part of the schizophrenic process. They are expressions of a progressive teleologic regression actualized by various forms of concretization. Dr. Arieti introduces us once again to the vicissitudes of paleologic thought and the Von Domarus principle. He ends the chapter by discussing a cognitive aberration he has named "awholism."

The fourth paper is a nice study on visual hallucinations by Frieske and Wilson. They set up three groups of patients: schizophrenic, organic and affective. Using an interview technique, they investigated certain details of the hallucinatory phenomena encountered by the patients in each of the groups. They found, among other things, that almost all schizophrenics with visual hallucinations have concomitant auditory experiences and that visual hallucinations alone were virtually restricted to the organic group. The schizophrenic patients tended to personalize their hallucinatory phenomena while visual hallucinations seen only with the eyes closed were restricted to organics.

The first section ends with a short paper by Rado. He emphasizes the importance of seeing schizophrenic symptomatology as the adaptive efforts of diseased human beings who struggle, but rarely succeed in achieving a tolerable existence.

The section on psychology contains five papers of varied content. Most are technical reports with complex methodology involving the manipulation of masses of clinical data. While not to be dismissed as academic exercises, some results fall short of obvious clinical application.

One of the high points of the book is the Hamilton lecture of schizophrenia given by Hoch. In less than 20 pages, Dr. Hoch does a remarkable job of bringing together the essentials for a discussion of what schizophrenia is all about and how it got that way. The section on neurochemistry and genetics contains five other papers. The first is an excellent, but brief summary on biochemical research by Kety.

The section on clinical research contains a number of useful articles. Lauretta Bender's discussion of childhood schizophrenia is a statement of her concept of "plasticity" and a good review of the subject. There is also another of the reports by Barbara Fish on the predictions of schizophrenia in infancy. The section ends with a paper on the incidence of schizophrenia in New York street gangs.

A review of pharmacotherapy by Lehmann is the first article in the therapy section. It is concise, well written and informative. In the following chapter Kalinowski discusses the role of ECT in the treatment of schizophrenia and speculates on the mechanims of action. The section ends with an article demonstrating increased levels of inhibition in schizophrenic patients given a stimulus-response task.

The final section has four papers. They more or less fit into the category of community aspects of schizophrenic illness. The cross-cultural classification paper by Zubin and Keitzman would have the most general interest.

Each section ends with a transcript of the discussion which followed the original presentation. Interesting questions are raised but often go unanswered. This is not very satisfactory for the reader.

There is an appendix (containing the names and addresses of members of the sponsoring association) and a good index. The physical format leaves something to be desired. Price: $19.75.

PAUL FREDERIC SLAWSON, M.D.

* * *

PATHOLOGY, Vols. I and II—5th Edition—Edited by W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P., Professor of Pathology and Chairman of the Department of Pathology, University of Miami School of Medicine; Director of the Pathology Laboratories, Jackson Memorial Hospital, Miami, Florida. The C. V. Mosby Company, St. Louis, Mo., 1966. 1439 pages, $21.00.

The fifth edition of this well-known textbook has been separated into two volumes, making it much easier to handle, as its total weight is 10 pounds. The portion dealing with General Pathology in Volume I can be used without having to hold or carry most of the sections treating the organ systems. The chapters on the cardiovascular, respiratory and urinary systems, however, are bound with those on General Pathology.

As in previous editions, a variety of specialists have contributed units dealing with the body systems of their particular interest and specialized knowledge. While the organization and general approach are those of a textbook for students, this multiple authorship has resulted in sufficiently authoritative discussions in many areas so that the work can serve as a reference for graduates in pathology or in other specialties. Disadvantages of this system include some loss of unity of approach, and duplication in certain areas, but for most these will be overbalanced by the benefits provided by the multiple contributing authors.

Changes from previous editions include more comprehensive consideration of ultrastructural features of disease and a greater emphasis upon viral and parasitic disease as compared with bacterial infections. Divisions of special pathology that are covered more completely than in most other textbooks of pathology are those on the skin, the skeletal system, the nervous system and the organs of special senses.

The type is set in two columns; subject references are up-to-date; the illustrations in general are well chosen and adequately reproduced.

Alvin J. Cox. M.D.

* * *

CURRENT DIAGNOSIS—A Biennial Volume of Clinical Diagnostic Methods and Evaluations—Edited by Howard F. Conn, M.D., Robert J. Clohecy, M.D., and Rex B. Conn, Jr., M.D. W. B. Saunders Company, Philadelphia, Pa., 1966. 843 pages, $19.00.

This book represents a newly introduced counterpart to the popular series of "Current Therapy" volumes. As indicated by its editors, it was conceived "in an effort to provide the physician with a convenient, authoritative source of information on today's best and most up-to-date methods of arriving at a precise understanding of the nature of a patient's illness." To achieve this goal, the symptoms and signs, physical findings, complications, laboratory tests and other procedures helpful in identifying a certain disease are epitomized by some 285 authorities. As might be expected in a compendium of this magnitude and with so many contributors, there are gaps. These stem in large part from necessary lack of depth and from individual variations in approach to diagnosis. Those who wish detail or desire fundamental references to basic diagnostic studies will not find them here. Nor will this collection of diagnostic features be of great help unless the physician has first determined for himself the nature of the disease which he suspects his patient to have. Despite these limitations, the practicing physician should find this volume a valuable reference source against which to check his diagnostic impressions and the studies he plans to make.

J. Edward Berk, M.D.

* * *

OPERABLE HEART DISEASE—Pathophysiology, Diagnosis, and Treatment—Howard D. Sirak, M.D., Associate Professor of Surgery and Head, Cardiovascular Service, Division of Thoracic Surgery, Ohio State University Hospitals, Columbus, Ohio. The C. V. Mosby Company, St. Louis, 1966. 130 pages, $12.50.

This monograph is a hurried review of the common cardiac lesions amenable to surgery. In the foreword it is indicated that the book is primarily intended for students, interns and residents. A book of this nature should, therefore, be complete, concise, and interesting. Certain chapters, specifically those involved with the postoperative care and fetal circulation do accomplish these ends. The brevity of the text on acquired and congenital problems fails to provide adequate discussion of the disease, differential diagnoses, electrocardiographic and catheterization abnormalities, and reasons for submitting such patients to surgery. There is some confusion in anatomical relationships through attempts to standardize all diagrams. The reviewer objects to over-simplification and colloquialisms such as hi, lo, and ducti. The book does provide a quick reference for the types of anomalies encountered at the operating table. To be important to the student, intern or resident, additional texts must be at hand in order to interpret some of the statements of the author.

* * *

CARCINOMA OF THE ALIMENTARY TRACT—Etiology and Pathogenesis—Edited by Walter J. Burdette, A.B., A.M., Ph.D., M.D., Professor and Head of the Department of Surgery and Director of the Laboratory of Clinical Biology, University of Utah College of Medicine; Surgeon-in-Chief, Salt Lake County Hospital; Chief Surgical Consultant, Veterans Administration Hospital, Salt Lake City, Utah. University of Utah Press, Salt Lake City, Utah, 1965. 233 pages, no price quoted.

There were 33 participants in this symposium of which 19 contributed a chapter to this book. Of the 28 chapters including the preface, 11 are devoted to a consideration of human alimentary tract neoplasms and seven to similar neoplasms in laboratory animals. The first five chapters consider the epidemiology of cancer of the esophagus, stomach, and large bowel in the Americas, U.S.S.R., Poland, and among the migrant populations of a number of countries. The striking variation in the incidence of G.I. tract cancer raises far more questions than are answered. Why, for example, is there a large socio-economic gradient for cancer of the esophagus, a lesser one for the stomach, and none for the large intestine and rectum? Why are all three forms of cancer more common among urban populations than in rural areas and why are there variations in the incidence of cancer of the esophagus, stomach, and large bowel varying with occupation and industry? The wide variations in the incidence of these cancers would seem to suggest environmental etiologies. If this were shown to be true, the possibility of prevention of many of these neoplasms becomes an appealing objective. When wide variations and incidences of these cancers occurs within a limited geographical region among rather isolated populations, genetic etiology may be of importance.

It is interesting that mice and rats, which have been close associates of man for centuries, rarely show cancers of the gastro-intestinal tract although other cancers may occur fairly frequently. One of the most interesting reports of spontaneous cancer of the glandular stomach of a rodent is dealt with by Katherine Snell. These cancers occurred in the African multimammate mouse, the Mastomys, and were first reported by Oettlé in 1957. The latter author gave an incidence of adenocarcinoma of the glandular stomach of these animals of 41 per cent among those dying of natural causes. Snell reports that the Mastomys at the National Institutes of Health showed carcinomas or precarcinoma lesions in 48 per cent of the males and 23 per cent in females. It may be significant that the diet fed to Oettlés' Mastomys contained 9.2 per cent of peanut meal which is frequently infected with Aspergillus flavus and this produces aflatoxins which are known to be potent G.I. tract carcinogens. Snell makes no mention of the diet of the N. I. H. colony of Mastomys. Tumors of the alimentary tract of hamsters and cats are discussed and experimental studies reported. The conclusion is reached that the high incidence of alimentary tract tumors in domestic cats may be due to environmental carcinogens. Weisburger discusses the interesting relationship between carcinogenic compounds and the areas of the alimentary tract in which they result in cancer development.

The frequently occurring discussion of the relationship between polyps and carcinomas of the colon is discussed by Burdette. He concludes that most cancers of the colon arise directly from the mucosa, independent of association with polyps but that the adenomous polyps can become malignant occasionally. Evidence is presented that colonic cancer may have a strong genetic factor in its causation. Strong evidence is presented that the association of blood group A and cancer of the stomach is causal. It seems reasonably clear from the data presented by Dennis that there is an increased risk of cancer of the colon in chronic ulcerative colitis. Cancer of the esophagus in man varies widely in incidence from the U.S.A. to France and Switzerland and the Island of Curaçāo to regions of South Africa and other countries. A great variety of environmental agents have been implicated in these differences but nothing conclusive is established. Likewise, the relationship between the use of tobacco and cancer of the esophagus and stomach is not too convincing.

The final 29 pages of the book are devoted to discussion and, in the opinion of this reviewer, contribute little to its value. This publication is attractively printed and bound, illustrations are of good quality and sufficient in number and the references are well selected. The short chapters make the book easy to read and the author and subject index appears to be complete. This book is a useful concise summary of the current knowledge of some aspects of cancer of the alimentary tract of man and a few laboratory animals but nothing outstandingly new is presented.

M. H. Simmers, M.D.

* * *

PATHOLOGY ANNUAL: 1966, Volume I—Series Editor, Sheldon C. Sommers, M.D.; Professor of Pathology, Columbia University College of Physicians and Surgeons; Associate Director of Laboratories, Francis Delafield Hospital, New York, New York; Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif. Appleton-Century-Crofts (Division of Meredith Publishing Company), New York, 1966. 387 pages, $12.00.

This volume is the first of the Pathology Annual Series; created according to its editor, Sheldon C. Sommers, to remedy an existing deficiency in pathology literature, and intended mainly for the practicing pathologist. The fourteen essays by distinguished pathologists are reviews or expositions on subjects of special interest and experience of each of the authors. While the approach in these essays is mainly histologic and cytologic, the clinical aspects of various disease processes are treated as well. Included in the volume are essays on an information processing system for pathology, cancer of the cervix, the adrenal, mesenteric vascular occlusion, the placenta, encephalitis, the pancreatic islets, and on the pathologist as a hospital biologist. Particularly outstanding, in the opinion of this reviewer, are the papers by Cochrane on "Vascular and Glomerular Inflammation: Mechanisms of Initiation and Mediation," by Aréan on "Schistosomiasis: A Clinicopathologic Evaluation," by Taylor on "Functioning Ovarian Tumors and Related Conditions," by Churg and Dach on "Diabetic Renal Disease: Arteriosclerosis and Glomerulosclerosis," by Sherwin on "The Identification of Lung Cancer and the Recognition of Favorable Variants," and a fascinating one by Hutt on "Buruli Ulcer, Subcutaneous Phycomycosis and Idiopathic Tropical Splenomegaly: Three Recent Aspects of Pathology in Africa."

Most of the essays are appropriately and well illustrated, and many include a number of electron photomicrographs. While these essays should be of interest mainly to pathologists, many physicians in other fields will find an abundance of information useful to them.

Stuart Lindsay, M.D.

* * *

ARTERIOGRAPHY—PRINCIPLES AND TECHNIQUES—Emphasizing Its Application in Community Hospital Practice—By Joseph L. Curry, M.D., and Willard J. Howland, M.D., Department of Radiology, Ohio Valley General Hospital, Wheeling, West Virginia. W. B. Saunders Company, Philadelphia, 1966. 328 pages, $14.00.

The authors have intended their monograph as "a brief introduction to the field of arteriography for the community radiologist." They have succeeded admirably in this purpose. For the general radiologist isolated from the university centers this book provides an excellent beginning guide. Each step in organization—including equipment, methods, hazards and diagnosis — is well covered.

Unfortunately, their approach to equipment and contrast materials is rather parochial, based it would seem on their own experience. The sections of the book devoted to diagnosis cover most of the pathology commonly encountered in a community hospital. However, the illustrations fall far short of an adequate quality. This is due in large part to the very small size of the individual photographs. As a diagnostic text this monograph would have much greater value if the illustrations were more adequate.

James E. Youker, M.D.

* * *

HERITABLE DISORDERS OF CONNECTIVE TISSUE—Third Edition—Victor A. McKusick, M.D., Professor of Medicine, The Johns Hopkins University School of Medicine; Physician, The Johns Hopkins Hospital, Baltimore. The C. V. Mosby Company, St. Louis, Mo., 1966. 499 pages, $18.50.

Recent years have witnessed a great surge of interest and advancement in medical genetics. Dr. McKusick has contributed significantly to these changes, especially related to the disorders discussed in this book. He is thus eminently well qualified to make the authoritative selection and interpretation of the vast literature summarized and presented in his book.

In the six years since publication of the second edition of this book, considerable new information on diseases of connective tissue has accumulated and this is reflected in the 166 additional pages of this new third edition. The general format has remained the same but now includes 12 chapters rather than the former eight. The first chapter summarizes genetic principles and will prove most useful to readers with a limited background in genetics. The second chapter reviews our current knowledge of connective tissue. For those persons not fully acquainted with these disciplines, an initial reading of the first two chapters will not only make more easy but also more meaningful the reading of the remainder of the book, which deals with specific disorders.

Chapters included in the previous edition and now rewritten or updated include: The Marfan Syndrome; the Ehlers Danlos Syndrome; Osteogenesis Imperfecta; and Pseudoxanthoma Elasticum. The earlier chapter on the Hurler Syndrome now has the title, The Mucopolysaccharidoses, reflecting increased understanding of the syndrome which now appears to include at least six separate and distinct disorders. The concluding Comments chapter has been almost tripled in length and subdivided into three new chapters: Other Genetic Disorders of Connective Tissue (including fibrodysplasia ossificans progressiva, osteopoikilosis, Leri's pleonosteosis, Paget's disease of bone, and certain other genetic disorders of the osseous skeleton); The Future in the Study of Heritable Disorders of Connective Tissue; and General Summary and Conclusions. Alkaptonuria now represents a separate chapter, as does the recently recognized disorder, homocystinuria, which probably has been frequently mistaken for the Marfan Syndrome in the past.

The extensive use of photographs and illustrations should greatly help clinicians in becoming more familiar with these diseases, as well as promote their more ready recognition. The extensive list of references (through part of 1965) makes this work a very good source book for those desiring recent information as well as for readers with historical interest in earlier publications. The index now includes over 14 pages (increased three fold from the previous edition) and greatly facilitates the localization of contained information.

The author notes in the preface that the book is especialy addressed to the general practitioner, the internist and pediatrician because these physicians probably are in the best position to evaluate the patient with reference to his family background. All physicians could readily understand the descriptions and discussions, and thus profit from reading the book. The question might be reasonably raised as to whether the average clinician should spend his limited time studying these generally uncommon diseases. For this reason the book may well serve the practitioner best as a reference book and I know of no better source to consult regarding the inherited connective tissue disorders.

ROBERT S. SPARKES, M.D.

* * *

MEDICAL DEPARTMENT, UNITED STATES ARMY IN WORLD WAR II (The Technical Services)—Medical Service in the Mediterranean and Minor Theaters—By Charles M. Wiltse, chief historian; Office of the Chief of Military History, Department of the Army, Washington, D.C., 1965. 664 pages; for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. $5.00.

It has been pointed out that much of history is written by history's winners and their accounts are usually cheerful reading. Winners minimize the mistakes inevitable in human enterprises and allot credit instead of sharing the blame. Such a record is this account of *Medical Service in the Mediterranean and Minor Theatres*. One is duly impressed by the enormity of the problem; the widespread operations; the diseases encountered and other bits of factual information of major concern to administrators. But one looks in vain for any recommendations for a system change which will prevent the myriads of operational and preparational errors (or lack of preparation) from occurring again.

To those of us who spent our time in this theatre from the invasion of North Africa, through Sicily, Italy, Southern France and Germany, very few of the problems concerning the working doctor are even mentioned let alone discussed. Many of the problems had been pointed out in civilian publications from experience gained in the Spanish Civil War and yet when the U.S. entered the war the training manual TM 8-108 was dated March 1924.

In time of war, it is the civilian who becomes the military doctor who bears the brunt of the actual medical care. While this volume is intended to be a history of the administrative problems of the medical department, it is disappointing to find little in the book with reference to the direct problems of the doctor.

ROY COHN, M.D.

VIRUSES INDUCING CANCER—Implications for Therapy—Edited by Walter J. Burdette, A.B., A.M., Ph.D., M.D., Professor of Surgery and Associate Director, M. D. Anderson Hospital and Tumor Institute, The University of Texas, Houston, Texas. University of Utah Press, Salt Lake City, Utah, 1966. 498 pages, no price listed.

The implications of the possibility of a virus etiology of malignant disease in humans are so vast that intense interest is aroused on the basis of the demonstration of viruses as causative agents of neoplastic disease in animals. This book is based on a conference (unfortunately, the time and place are not stated) and contains the recent contributions of many of the most active virologists in the field of oncology, but does not include a discussion of chemotherapy or of surgery. As a consequence the language is largely that of the virologist. An adequate review is made of most subjects discussed. The implications for therapy stated in the subtitle are not for immediate application; however, physicians might obtain insight into developments of the future from reading selected chapters in this book. The surgeon might be interested in learning that preneoplastic lesions can be used to assay mammary tumors of mice. The immunologist and hematologist might consider the implications of the fact that congenitally infected chickens fail to develop antibodies to the avian leucosis viruses and consequently virus persists throughout the lifetime of the animal. Infection later in life, however, can be prevented by vaccination and serum treatment may modify the disease.

One of the more exciting discoveries in recent years has been that of Rubin who found that strains of Rous Sarcoma Virus are defective and will only produce mature virus particles with the aid of a helper virus. The resulting virus carries the protein coat, and consequently the antigenicity, of the specific helper. Melnick and Rapp have described hybrid infections with adenoviruses and a monkey virus (SV40) which also have profound implications on the use of live virus vaccines in man and the possibility of transmission of infections to human.

The book is well reproduced. The discussion for the conference is placed at the end of the book and gives the reader an opportunity to "listen in" on some of the questions the experts have on their colleagues' work.

STEPHEN J. SELIGMAN, M.D.

* * *

IMMUNOPATHOLOGY—IV International Symposium, held at Monte Carlo (Principality of Monaco) February 1965. Sponsored by the World Health Organization, the Council for International Organizations of Medical Sciences, and the National Foundation—Edited by Pierre Grabar, Paris, and Peter A. Miescher, New York. Grune & Stratton, Inc., New York, 1966. 467 pages, $19.75.

The 31 papers in this text were presented at an International Congress in February of 1965. Although already one year out of date, this text represents the most recent developments in a rapidly burgeoning field. Papers are divided into five chapters: (1) research on tumor-specific antigens, (2) histo-compatibility antigens, (3) multiple myeloma and amyloidosis, (4) immunopathology of various organs and (5) mechanisms of immune vasculitis. There are extensive bibliographies for each paper, as well as discussions of each chapter. Any scientist involved in any one of these five areas of immunopathology will find this text a valuable addition to his library. To the practicing clinician or medical student the chapters on immunopathology of various organs and mechanisms of immune vasculitis provide valuable insight into clinical problems.

There are excellent papers dealing with the distinctions between viral and tumor-specific antigens. As is a fault of so many publications of the proceedings of International Congresses, not all the papers are of comparable quality. The great variety of topics covered necessitates that some of the topics are presented less extensively than others. Furthermore, six of the papers are in French, and some of the translations are inadequate. Nonetheless, the text represents the most recent work of the very best investigators in this field and is to be highly recommended. Indeed, all scientists active in the broad field of Immunology will find this text of value.

EUGENE V. BARNETT, M.D.

* * *

RADIOGRAPHIC EXAMINATION IN BLUNT ABDOMINAL TRAUMA—James J. McCort, M.D., Director of Radiology, Santa Clara County Hospital, San Jose, Calif.; Clinical Associate Professor of Radiology, Stanford University Medical School, Palo Alto, Calif. W. B. Saunders Company, Philadelphia, 1966. 252 pages, $10.50.

James McCort has produced a splendidly readable work on blunt abdominal trauma. His style is enviably spare and concise. A logical, orderly exposition of methods of radiographic study and general findings in hemorrhage and trauma is followed by separate chapters on lacerations of the spleen, liver, mesentery, intestinal tract, pancreas, diaphragm, kidney and ureter, bladder, urethra and retroperitoneal hemorrhage. The role of angiography is well shown, as are other special procedures. These include radioisotope scanning, pneumoperitoneum, and intraperitoneal instillation of diatrizoate. The publisher may share praise for top quality reproductions of the radiographs, which successfully depict some subtle changes of importance. The book should be of interest and value to general surgeons and urologists as well as radiologists.

ROBERT B. ENGLE, M.D.

* * *

HERNIA—Lloyd M. Nyhus, M.D., F.A.C.S., Professor, Department of Surgery, and Henry N. Harkins, M.D., Ph.D., F.A.C.S., Professor and Chairman of the Department of Surgery, University of Washington School of Medicine, Seattle, Editors. Foreword by Sir John Bruce, C.B.E., T.D., M.B., Ch.B. (Ed.), F.R.C.S. (Ed.), Hon. F.R.C.S. (Eng.), Regius Professor of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland. J. B. Lippincott Company, Philadelphia and Montreal, 1964. 836 pages, $28.50.

During the ten years immediately preceding this very large book on hernias of all types, the senior editors helped to develop and popularize the preperitoneal approach for groin hernias. Presumably it was as a result of their experiences with this relatively new surgical approach, that they were inspired to assemble the various contributors to the subject of hernia generally. The first 314 pages are devoted exclusively to groin hernia, and if there is a valid criticism of the entire work, it is in this section where the editors' bias is so apparent. The Bassini operation, for example, gets no attention other than passing mention, while the preperitoneal approach is lavishly praised. Despite chapters on the Halsted I, the Cooper's ligament repair, and other anterior approaches, Dr. Harkins summarizes the entire groin section by stating that "the conventional anterior approach to hernioplasty might even be compared to the birth deliveries of the Middle Ages performed under a modesty blanket." In view of other recent reports of a high recurrence rate in direct inguinal hernias by this approach, this reviewer is not at all certain that the more conventional anterior approaches deserve this criticism. On the other hand, the lengthy anatomical dissertation on the anatomy of the groin and the preperitoneal operation should inspire others, as it did the reviewer, to try the new approach. Not only is it a unique experience, but it almost certainly will prove to be a useful technique to all surgeons using it under certain circumstances.

Despite this criticism, the book is generally stimulating and informative. Drs. Nyhus and Harkins have assembled an extremely distinguished group of contributors, most of whom are widely known experts on the topics they write about. After each chapter there is an editorial comment, and other special comments by other authorities who stress certain points already made, or raise others pertinent to the subject. This particular manner of presentation, directed as it is toward experienced surgeons rather than medical students, only serves to make each chapter more interesting, and to the reviewer at least, enhances the value of the book considerably.

Other sections besides groin hernias include ventral hernia, diaphragmatic hernia, internal hernia, pelvic hernia, general aids to repair, and finally miscellaneous considerations. Literally no subject concerning hernia is too small to receive attention. There are chapters on sciatic hernia, Spigelian hernia, hernias in the young, hernias in the aged. The use of the various prosthetic materials including fascia lata grafts, nylon, tantalum, and marlex mesh are all thoroughly covered. Chapters entitled "Medico-legal aspects of hernia," "Industrial hernia," and "Anesthesia for hernia repair" illustrate the broad coverage accorded every aspect of hernia repair.

The just under 200 pages devoted to diaphragmatic hernia repair make that subject the second most thoroughly explored area in the book. All of the controversial aspects of the subject—the physiology of the so called lower esophageal sphincter, the various approaches for repair, and the diverse operations including even gastropexy and fundoplication are covered.

The reviewer considers this entire volume an outstanding contribution to the surgical literature, and would recommend it to every surgeon performing hernia repairs.

FREDRICK W. MARX, JR., M.D.

* * *

TODAY'S HEALTH GUIDE—A Manual of Health Information and Guidance for the American Family—Edited by W. W. Bauer, M.D. Published by the American Medical Association, Chicago, Illinois, 1965. 624 pages, $5.95.

The AMA's new health manual, *Today's Health Guide,* is neither an "old-fashioned" doctor's book nor a true encyclopedia. It is a gathering of selected topics, condensed from the enormous mass of knowledge about health which the editors and authors believe will be most useful to the average American.

Divided into 15 parts, it covers *The Home as a Health Center, Health and Your Family, The Wonderful Human Body, Safeguarding Your Health, Mental and Emotional Health, Recreation and Relaxation, Safety, Medical Services for the Family, When You Need a Doctor, Dangerous and Disabling Diseases, Surgery Today, The Proper Use of Drugs, Physical Handicaps, Community Health,* and *Keeping Posted* on medical history, progress and folk lore.

Such a book, which tries to be all things to all people, necessarily is limited in how much it can offer to anyone. Many of the chapters are written for doctor consumption and others in such fashion that doctors will understand them better than the public. All in all, however, it is a fine effort. There is good, understandable advice on everything from Emergency First Aid to Home Nursing Care, from sex education to calories.

Physicians will do well to follow the AMA's recommendation and keep a copy in their reception rooms, as well as urge their patients to buy it.

EDGAR WAYBURN, M.D.

SHOULDER PAIN—Rene Cailliet, M.D., Chief of Department of Physical Medicine, Southern California Permanente Medical Group; Associate Clinical Professor, University of Southern California School of Medicine, Department of Physical Medicine and Rehabilitation; and Department Head, Physical Medicine, Kaiser Foundation Hospitals, Southern California. F. A. Davis Company, Philadelphia, Pa., 1966. 115 pages, $3.00 (Paperback).

This is the third in a series of paperbacks by this author. The previous ones on "Low Back Pain Syndrome" and on "Neck and Arm Pain."

This present booklet concerns itself with the functional anatomy of the shoulder girdle, with musculoskeletal conditions, with traumatic conditions, with biceps tendinitis, with neurological causes of shoulder pain.

There are many excellent teaching diagrams which emphasize the text and make this an easily readable and easily understandable booklet.

It is always difficult to specify the various causes of shoulder pain and the author has done a magnificent job in describing the various entities.

Treatment is directed along the lines of exercise and local injections rather than heat and massage.

This book, as well as the two former companions, should be in the library of every orthopedist, physiatrist, and other physicians who deal frequently with painful shoulders.

S. MALVERN DORINSON, M.D.

* * *

THE CELL—Its Organelles and Inclusions—An Atlas of Fine Structure—Don W. Fawcett, M.D., Hersey Professor of Anatomy, Harvard Medical School. W. B. Saunders Company, Philadelphia, Pa., 1966. 448 pages, $11.00.

An electron photomicrograph is doubtless worth a thousand words for those interested in serious study of subcellular anatomy. In this sense Professor Fawcett has condensed more than 240,000 words into 448 pages containing 240 electron photomicrographs of very high quality. Although not all the major organ systems are illustrated the breadth of coverage is sufficient to satisfy the inquisitive practitioner in any area of medicine.

The book is divided into three parts including The Cell Organelles, The Cell Inclusions and The Cell Surfaces. Brief but lucid introductions to each part will allow understanding by physicians who departed medical school long before the electron microscope allowed the stimulating correlation of subcellular structure with function.

A primer such as this will be of great background value for all those endeavoring to keep abreast of the medical literature which almost monthly contains descriptions of diseases which seem associated with defects in lysosomes, mitochondria, Golgi complexes, muscle filaments and other structures rarely emphasized in histology courses only a few years ago. Fortunately for the serious student of biology or medicine the pictures are not limited to human subcellular anatomy. Rather a variety of species are used to illustrate morphologic features which may or may not have counterparts in the human, as well as to demonstrate a seeming diversity of function in what appear to be very similar structures.

The general references appended to each section provide easy access to current, more detailed literature on the subjects discussed. This book could be valuably used with J. A. G. Rhodin's "An Atlas of Ultrastructure" which provides electron photomicrographs of most mammalian organs with but very little attempt at correlation with the known biochemistry of the organ under discussion.

J. B. PETER, M.D., Ph.D.

block end runs

LOMOTIL® tablets liquid

Each tablet and each 5 cc. of liquid contains:

diphenoxylate hydrochloride . . . . (Warning: May be habit forming)	2.5 mg.
atropine sulfate	0.025 mg.

tackles the problem of diarrhea directly

Effectiveness—Physiologic evidence indicates that Lomotil acts directly on the smooth muscle of the bowel to lower motility and control diarrhea. This action is unsurpassed in promptness and efficiency.

Convenience—Lomotil is available as small, easily carried, virtually tasteless tablets and as a pleasant, fruit-flavored liquid.

Versatility—The therapeutic efficiency, safety and convenience of Lomotil may be used to advantage alone or adjunctively in diarrhea associated with:

- **Functional hypermotility**
- **Irritable bowel**
- **Acute infections**
- **Gastroenteritis and colitis**
- **Malabsorption syndrome**
- **Regional enteritis**
- **Ileostomy**
- **Ulcerative colitis**
- **Food poisoning**
- **Drug therapy**

For correct therapeutic effect
Rx correct therapeutic dosage

Dosage: The recommended initial daily dosages, given in divided doses until diarrhea is controlled, are:

Children: Total Daily Dosage

3-6 mo. . .	½ tsp.* t.i.d. (3 mg.)
6-12 mo. .	½ tsp. q.i.d. (4 mg.)
1-2 yr. . . .	½ tsp. 5 times daily (5 mg.)
2-5 yr. . . .	1 tsp. t.i.d. (6 mg.)
5-8 yr. . . .	1 tsp. q.i.d. (8 mg.)
8-12 yr. . .	1 tsp. 5 times daily (10 mg.)
Adults: . .	2 tsp. 5 times daily (20 mg.) (or 2 tablets q.i.d.)

*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

Precautions: Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is a Federally exempt narcotic preparation of very low addictive potential. Lomotil should be kept out of reach of children since accidental overdosage may cause severe respiratory depression. Recommended dosages should not be exceeded. Lomotil should be used with caution in patients with impaired liver function and in patients taking addicting drugs or barbiturates. The subtherapeutic amount of atropine is added to discourage deliberate overdosage.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

SEARLE *Research in the Service of Medicine*

...but doctor,
I eat like a bird!

IN WEIGHT CONTROL
OBETROL®

Each OBETROL-10 tablet contains: Methamphetamine Saccharate 2.5 mg., Methamphetamine Hydrochloride 2.5 mg., Amphetamine Sulfate 2.5 mg., Dextro-amphetamine Sulfate 2.5 mg. (OBETROL-20 tablets contain twice this potency) Pat. #2748052.

This combination of amphetamines may be useful as an adjunct in the management of certain forms of obesity where an appetite depressant is indicated.

CONTRAINDICATIONS: Hypertension, advanced arteriosclerosis, coronary artery disease, cardiac arrhythmias, peripheral vascular disease, states of undue restlessness, anxiety, excitement, agitated depression, hyperthyroidism, idiosyncrasy to amphetamine, concomitant administration of a monoamine oxidase inhibitor. PRECAUTIONS: Use with caution in individuals with anorexia, insomnia, vasomotor instability, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies, and individuals who are known to be hyperreactive to sympathomimetic agents, or emotionally unstable individuals who are known to be susceptible to drug abuse. Certain monoamine oxidase inhibitors may potentiate the action of Obetrol. SIDE EFFECTS: The most common side effects attended with the use of amphetamines include nervousness, excitability, euphoria, insomnia, dryness of mouth, nausea, vertigo, constipation, and headache. DOSAGE AND ADMINISTRATION: Initial adult dose is one-half to one 'Obetrol-10' tablet daily, preferably one-half to one hour before meals. This may be gradually increased to one 'Obetrol-10' or 'Obetrol-20' tablet one to three times daily as indicated. SUPPLIED: Tablets scored, in bottles of 100, 500, and 1000.

REQUEST SAMPLES AND LITERATURE

OBETROL PHARMACEUTICALS
Div. of Rexar Pharmacal Corp. Brooklyn, N.Y. 11207

OBETROL PHARMACEUTICALS • BROOKLYN, N.Y. 11207
Dr. ____________________
Address ____________________
City ____________ State ________ Zip ______

BOOKS RECEIVED

(Continued from Page 32)

School of Medicine of Wake Forest College, Winston-Salem, North Carolina; formerly Professor and Head of the Department of Radiology, University of Arkansas School of Medicine, Little Rock, Arkansas. With the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia), M.D., Research Associate, Department of Radiology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. W. B. Saunders Company, Philadelphia, Pa., 1966. The set of two volumes, $38.00. Vol. I singly, $18.00; Vol. II singly, $20.00.

A SEARCH FOR GENETIC EFFECTS OF HIGH NATURAL RADIOACTIVITY IN SOUTH INDIA—H. Grüneberg, G. S. Bains, R. J. Berry, Linda Riles, C. A. B. Smith and R. A. Weiss. Medical Research Council, Special Report Series No. 307. Published by Her Majesty's Stationery Office, London, 1966. Agents in the United States for Her Majesty's Stationery Office—British Information Service (Sales Section), 845 Third Avenue, New York, N.Y. (10022), 59 pages, $2.20.

SYNOPSIS OF NEUROLOGY—Second Edition—Francis M. Forster, B.S., M.D., Professor and Chairman, Department of Neurology, University of Wisconsin School of Medicine, Madison, Wisconsin. The C. V. Mosby Company, St. Louis, 1966. 218 pages, $7.50.

Many Football Knee Injuries Preventable

The prevention of knee injuries in football should rate priority attention, even though protecting the knee is difficult.

A joint statement by the National Federation of State High School Athletic Associations and the American Medical Association's Committee on the Medical Aspects of Sports offers suggestions for greater player protection.

The best protection, the statement said, may be the player's own efforts to build strength in leg muscles supporting the knee. These are the knee's only supporting structures whose strength can be improved.

It is a paradox that the knee—considered one of the strongest joints in the body—is the most commonly injured major joint in contact sports, the statement noted. This is partly due to the knee's unusual structure. It is more than a mere hinge; the leg must rotate as the joint hinges.

This versatile joint movement makes possible the crowd-thrilling action of a dodging, weaving football "scat back." On the other hand, the complexity of the knee's structure also makes the player vulnerable to disabling injury.

Bad practices cause many knee injuries, the statement said, and such practices can only be eliminated by better coaching and strict control of the game. These practices include clipping, blind-side blocking, piling-on after tackles, and unnecessary contact after an official's whistle has sounded.

Knee pads help avoid bruise-type injuries, but protective equipment otherwise offers primarily only psychological benefits, the statement said.

The player can help prevent injury by following his coach's advice to shorten and quicken his

(Continued on Page 44)

"The response in most cases is dramatic..."

Lowell, J.B.: New England J.Med. 269: 798, 1963.

When Lowell added phenylbutazone to his usual immobilization and rest measures for the treatment of acute shoulder bursitis, he found "The response is dramatic and occurs within forty-eight to seventy-two hours, and occasionally as early as twenty-four hours. There is rapid loss of pain and concomitant increase in available motion".

quently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possible side effects.

Confusional states, hyperglycemia, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Average Dosage: Initially, give 400 mg. daily (one tablet or capsule q.i.d.), reducing this, if possible, when a favorable therapeutic effect has been obtained. If after one week there has been no response, discontinue the drug.

For complete details, please refer to full prescribing information. 6509-V(B)

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

BU-4513

Butazolidin® alka Geigy

Each capsule contains: Butazolidin®, phenylbutazone, 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate, 150 mg.; homatropine methylbromide, 1.25 mg.

What does the future hold?

when residential treatment is indicated . . .

DEVEREUX SCHOOLS

UNDER THE DEVEREUX FOUNDATION
A NONPROFIT ORGANIZATION

Helena T. Devereux
Founder and Consultant

Edward L. French, Ph.D.
President and Director

FOR INFORMATION AND LITERATURE

Santa Barbara (Box 1079), California
Keith A. Seaton, Director of Admissions

Devon, Pennsylvania and Rutland, Massachusetts
Charles J. Fowler, Director of Admissions
Devereux Schools, Devon, Penna. 19333

Victoria (Box 2666), Texas
Richard D. Grant, Registrar

Many Football Knee Injuries Preventable

(Continued from Page 40)

stride when in the zone of action. This lessens the time a foot is on the ground—the only time a knee injury can occur.

Some football shoes now have cleatless heels, an effort to prevent knee injury by giving the foot more freedom of movement. Results to date are encouraging, but continued study is recommended to learn more specifically the relative advantages of cleatless heels, the statement said.

If it were possible, the best way to prevent knee injury would be to select only athletes who were bowlegged and pigeon-toed, the statement noted. These leg alignments permit the least possible stress on the knee.

Beyond such an impractical solution, the best protection remains adherence to good practices, strict rule engorcement, and building-up of strength in the thigh, hamstring, and calf-muscles.

Adverse Reaction—Coincidental or Causal?

Thus we see that panic, misinterpretation, or just plain ignorance still form the basis of judgments about the safety of our newer drugs. Clinicians are still not used to thinking in terms of the huge number of individuals taking a particular drug, and the opportunity this affords for coincidental events which may be mistaken for casual relationships. If physicians do not keep this inevitable possibility in mind, they may end up treating coincidences instead of patients—an occupation of doubtful utility and poor prognosis.—Joseph W. Goldzieher, M.D., in *Texas State Journal of Medicine,* (62:37), May 1966.

Why Is a Driver Like a Prescriber?

We live in an age of therapy with potent drugs, and new weapons are coming to hand every year. These changes are to be welcomed; we cannot put back the clock even if we should wish to do so. The problems now posed by motor cars and drugs are in many ways similar. We must ensure that the price of advance is not too high and that accidents are reduced to a minimum by foresight and care. Both are examined, licensed, and periodically reviewed. Roads and lines of communication of information are improved. The manufacturers are exhorted to introduce the latest safety devices and tests. However, in the final analysis, most depends on the driver and prescriber.—G. M. Wilson, M.D., in *British Medical Journal,* (1:1068-1069), April 30, 1966.

California
Medicine

Earlier Diagnosis of Cervical Cancer

An Analysis of Reports to the California Tumor Registry from 1942 to 1963

GEORGE LINDEN, M.P.H., AND JOHN E. DUNN, JR., M.D., *Berkeley*

■ *The mortality rate for cervical cancer in California declined during the period 1950-64. Indirect evidence shows that the incidence is also declining, but it is difficult to assess this decline because of the effect of the increasing use of cytologic examination on incidence rates for cervical cancer.*

Cervical cancer, in the 57 hospitals reporting to the California Tumor Registry, is being diagnosed at an earlier stage than in previous years. The proportion of cases diagnosed with the lesion still in the in situ stage rose from zero in 1942 to 56 per cent in 1963, and invasive cervical cancer, as a proportion of all invasive cancer in women, decreased from 15 per cent to 9 per cent. There is wide variation among hospitals in the proportion of cervical cancer cases that are in situ at time of diagnosis.

MORTALITY IN CALIFORNIA due to cancer of the cervix has been decreasing for many years. Recorded mortality rates show a steady decline between the years 1950 and 1964, and there is indirect evidence that the decrease in mortality rates started at least 10 years earlier. As shown in Chart 1, the mortality from cancer of the cervix declined from 11.3 per 100,000 in 1950 to 7.5 in 1964, a reduction of one-third in 15 years. This decrease was not due to any change in the age distribution of the population, as can be seen in Table 1. The mortality rates for each age group under 65 show a pronounced decline between 1950 and 1964. For persons 65 years of age and over, the risk of dying of cancer of the cervix remained constant during the decade 1950 to 1960, but then declined. A general decline in mortality due to cervical cancer has also been noted in other reports.[4]

Effect of Cytologic Examination on "Incidence"

Several investigators have reported sizable decreases in "incidence" rates for cervical cancer.[2,6] An *incidence rate* is defined as the number of new cases occurring in a population during a specified time period—usually per 1,000 or 100,000 persons per year. A *prevalence rate* is defined as the number of cases existing in a given population at a specific time, regardless of time of onset. Since the event of a disease is usually defined at the time of diagnosis, the validity of incidence or prevalence rates is contingent upon,

---

From the California Cancer Field Research Project, California State Department of Public Health, Berkeley.

Presented as part of an Interagency Conference on Cancer Diagnosis, Treatment and Control in California at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: California Tumor Registry, California State Department of Public Health, 2151 Berkeley Way, Berkeley 94704 (Mr. Linden).

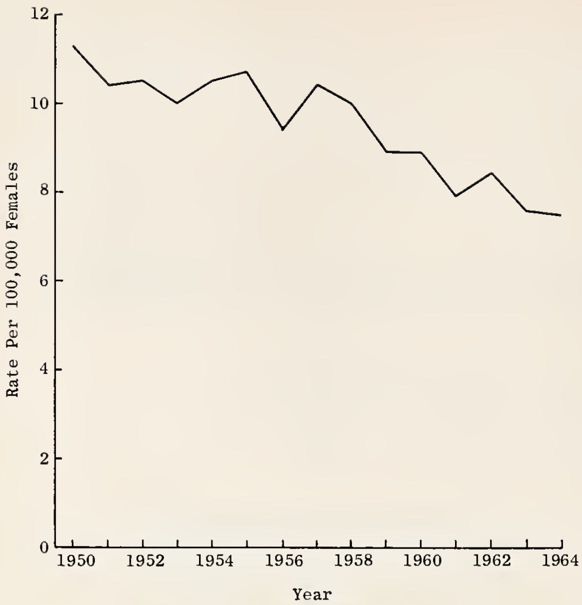


Chart 1.—Death Rates from Cancer of the Cervix, by Year, California, 1950-64.

among other things, the stability of the methods used in diagnosis. The introduction of a new technique, such as the Papanicolaou test for cervical cancer or mammography for breast cancer, enables physicians to diagnose cases earlier than had previously been possible. Cytologic examination not only increases the total number of cervical cancer cases by discovering cancer while it is still in situ, but also results in the diagnosis of cases that represent the prevalence of preclinical invasive disease. The changing proportion of cervical cancer cases diagnosed before invasive disease is clinically diagnosable distorts the "incidence" of invasive disease, since lesions are being detected earlier in their development than they would be under the clinical practices existing before cytologic examination came into use. The initial result is a massing of cases that represent a combination of incident and prevalent disease for the first few years; this in turn should be followed by a "deficit" of invasive disease in future years when the effect of identifying and treating in situ and preclinical invasive disease has had its effect.

It can thus be seen that the pattern of detection of cervical cancer has been profoundly changed by the introduction and promotion of cytologic screening. Any discussion or analysis of cervical cancer incidence rates must be related to the ever increasing use of the examination first demonstrated by Papanicolaou and Traut over 20 years ago as a means of diagnosing unsuspected cancer of the cervix.

Cervical Cancer in California

Data from the California Tumor Registry illustrate some of the changes that have occurred. The California Tumor Registry now contains records of more than 275,000 cases dating back to 1942. It is a central registry receiving abstracts of 20,000 cancer cases annually from 57 participating hospitals in California—approximately one-third of all cancer cases occurring in the state each year. Hospitals participating in the Registry constitute a cross-section of the different types of hospitals in the state where cancer is being diagnosed and patients treated. The cases reported are therefore more nearly representative of the average cancer patient than the cases seen in teaching hospitals or cancer centers. A fuller description of the Registry and its operation is contained in the monograph *Cancer Registration and Survival in California.*[5]

During 1942-61 a total of 99,037 cases of cancer in women first diagnosed in the participating hospitals were reported to the Registry. These include 5,251 cases in situ at various tissue sites, of which 4,141 (79 per cent) were in the uterine cervix. Chart 2 shows the increase of in situ cervical cancer as a proportion of all cervical cancer cases between the years 1942 and 1963. None of the 335 cervical cancer cases diagnosed in 1942 (with stage known) were diagnosed while still in the in situ stage. The proportion of cases diagnosed while still in situ increased slowly at first, reaching

TABLE 1.—*Death Rates (per 100,000 female population) from Cancer of the Cervix by Age California: 1950, 1955, 1960, 1964*

	AGE						
YEAR	*Under 25*	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75 and over*
1950	*	3.8	13.2	23.7	31.2	28.1	41.5
1955	*	2.3	13.3	22.2	28.0	31.0	43.2
1960	*	2.0	9.0	19.0	23.5	28.8	41.1
1964	*	2.1	7.8	15.9	20.6	22.7	32.5

*Rates were not computed for less than five deaths.

TABLE 2.—*In Situ Cervical Cancer Cases as a Proportion of Total Cervical Cancer Cases by Age and Year Group California Tumor Registry, 1945-61*

YEAR GROUP	AGE *Under 25*	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75 and over*
1945-46	0.0	3.1	1.8	1.0	0.0	0.9	0.0
1950-51	30.0	30.2	18.2	10.0	3.3	3.9	1.8
1955-56	60.5	45.1	35.6	21.4	14.8	9.5	2.1
1960-61	89.6	80.7	69.8	47.2	27.5	26.0	13.8

10 per cent by 1950 and 22 per cent by 1955. The increase was more pronounced after 1955. By 1960, 55 per cent of the 1,497 cervical cancer cases were in situ at time of diagnosis. In the next three years, ending in 1963, there was a leveling off between 55 per cent and 60 per cent in the proportion of cases that were in situ.

Does this represent a limit of the proportion of cervical cancer cases that can be diagnosed in the in situ stage? Evidence from one survey indicates that probably only about half of the women in California have had cytologic examinations at least once.[3] If this is true, there is ample room for improvement and the proportion of cervical cancer cases diagnosed while still in situ may become much higher than 55 to 60 per cent.

The increase in the proportion of in situ cases occurred at all ages, but not uniformly. Table 2 shows that for women under 25 the proportion of cervical cancer cases that were in situ at the time of diagnosis had risen to almost 90 per cent by 1960-61. This proportion decreased as age increased; in fewer than 15 per cent of the women 75 years of age or older was the lesion in situ when diagnosed.

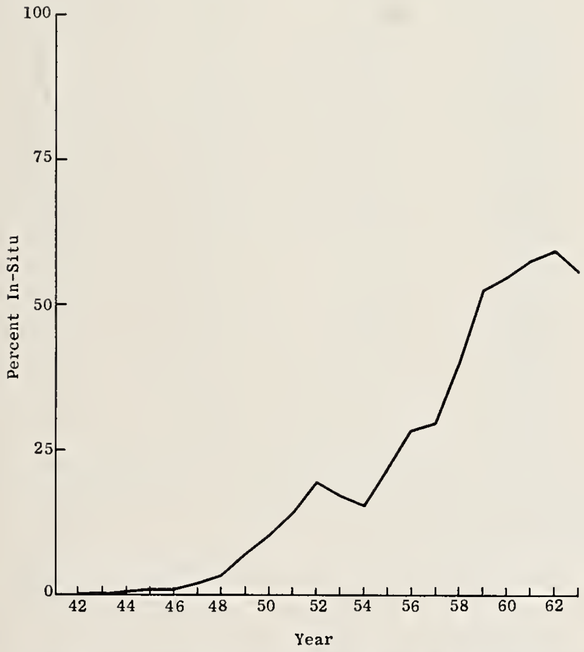


Chart 2.—In Situ Cervical Cancer Cases as a Proportion of Total Cervical Cancer Cases, by Year, California Tumor Registry, 1942-63.

Table 3 shows that invasive cervical cancer, as a proportion of all invasive cancers in females, has declined steadily. In 1942 it made up 15 per cent of all cancers in females; by 1961 it was only 9 per cent. This recorded decline is probably understated, since cytologic examination, as previously mentioned, has a double effect. Discovery at the in situ stage removes not only potential invasive cases from the population, thus reducing the number of invasive cases that would have occurred in the future—it also picks up invasive cases at a stage at which they otherwise would have gone unnoticed at the time of examination. The result is an immediate increase in the number of invasive cases found. The effect of earlier diagnosis of preclinical invasive cancer on the number of invasive cases being found will tend

TABLE 3.—*Invasive Cervical Cancer Cases as a Proportion of All Female Invasive Cancer Cases by Year California Tumor Registry, 1942-61*

YEAR	*PER CENT*
1942	14.8
1943	13.7
1944	14.6
1945	14.0
1946	13.3
1947	12.7
1948	13.1
1949	13.1
1950	12.6
1951	10.9
1952	10.7
1953	10.4
1954	10.9
1955	9.5
1956	10.3
1957	11.0
1958	10.4
1959	9.5
1960	9.3
1961	9.4

to disappear as the proportion of women who are being screened reaches a stable point, and the decline in the relative occurrence, and even in the absolute occurrence, of invasive cervical cancer should become even greater—to the extent that the in situ stage is a precursor of the invasive stage.

Spread of Disease at Time of Diagnosis

Increased use of cytologic screening, plus the emphasis on early diagnosis, has also affected the extent of spread of the disease at time of diagnosis. Table 4, excluding in situ cases, shows that the proportion of invasive cases that were localized at time of first diagnosis rose from 39 per cent in 1942 to 54 per cent in 1963. (Cases in the California Tumor Registry are classified according to the extent to which the tumor has progressed, as determined by all diagnostic and therapeutic evidence obtained during the time of the first course of treatment.) Cases in which there was regional spread decreased from 46 per cent to 31 per cent. There was no change in the proportion of cases with remote metastasis. It is difficult to assess accurately the role that cytologic screening played in these changing proportions, but there is little doubt that the entire pattern of cervical cancer has been shifted over to an earlier stage of disease at the time of first diagnosis.

Table 5 shows the trend in the proportion of invasive cases that are localized. Each age group between age 25 and 74 shows an increase, over the years, in the proportion of localized cases. The pattern for those under 25 years of age is irregular due to the small number of cases. As might be expected, the increase in localized cases is greater for younger women, for whom cytologic screening has been most extensively used, than for older women.

Variation in Use of Cytologic Examination

The use of cytologic screening for early detection of cervical cancer is not uniform. Results of a Gallup poll in 1961 was interpreted as showing that only 30 per cent of women in the United States had had the Papanicolaou test at least once.[3]

TABLE 4.—*Per Cent Stage Distribution of Invasive Cervical Cancer Cases by Year California Tumor Registry, 1942-63*

YEAR	*NUMBER OF STAGED INVASIVE CASES*	*PER CENT OF STAGED INVASIVE CASES*			
		Total	*Localized*	*Regional*	*Remote*
1942	335	100.0	38.8	46.0	15.2
1943	330	100.0	43.0	40.3	16.7
1944	350	100.0	43.4	43.7	12.9
1945	347	100.0	35.2	47.8	17.0
1946	400	100.0	36.8	48.0	15.2
1947	434	100.0	44.7	41.5	13.8
1948	441	100.0	38.8	45.8	15.4
1949	480	100.0	51.2	34.2	14.6
1950	503	100.0	44.7	36.6	18.7
1951	499	100.0	53.1	29.3	17.6
1952	534	100.0	47.2	34.8	18.0
1953	560	100.0	47.9	36.8	15.4
1954	609	100.0	44.3	37.4	18.2
1955	575	100.0	48.0	35.7	16.3
1956	645	100.0	51.2	34.1	14.7
1957	726	100.0	52.5	33.6	13.9
1958	689	100.0	51.4	35.6	13.1
1959	624	100.0	54.5	30.4	15.1
1960	678	100.0	51.5	36.6	11.9
1961	652	100.0	56.7	34.5	8.7
1962	734	100.0	52.0	33.8	14.2
1963	767	100.0	54.0	30.8	15.3

TABLE 5.—*Localized Cervical Cancer Cases as a Proportion of Invasive Cervical Cancer Cases by Age and Year Group California Tumor Registry, 1945-61*

YEAR GROUP	*AGE*						
	Under 25	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75 and over*
1945-46	100.0	39.7	41.7	36.4	33.7	28.7	34.3
1950-51	71.4	66.0	57.4	51.2	44.0	35.6	23.2
1955-56	86.7	72.9	59.8	50.2	39.4	38.7	26.6
1960-61	75.0	67.8	66.3	56.2	49.3	43.4	33.6

In Alameda County, California, this proportion was reported to be about 50 per cent in the Spring of 1962,[3] and in San Diego County, California, where the test has been strongly promoted, 62 per cent of the women in San Diego City (by 1961) and 72 per cent of the women outside the city (by 1962) had been tested at least once.[1,3]

This lack of uniformity in the use of cytologic examination is also reflected in the experience of the hospitals participating in the California Tumor Registry. The hospitals reporting cancer cases to the Registry are diverse: Large and small, teaching and non-teaching, private and public, urban and rural. A rough measure of how much (or how little) cytologic screening was used in examination of the women with cervical cancer reported from each of these hospitals, is the ratio of in situ cases to the total number of cases.

Chart 3 shows the wide range in the proportions of in situ to total cervical cancer cases for 48 of the 57 hospitals (the others are very small with few or no cases). The larger bars (white) on the chart, representing the proportion of cervical cancer cases that were reported as in situ in 1960-61, indicate that invasive cervical cancer is becoming fairly uncommon in a large portion of the reporting hospitals. In situ cancers constituted more than 70 per cent of the total cervical cancer cases in one-third of the 48 hospitals. At the other end of the scale, the picture is not very encouraging—the great majority of women presenting with cervical cancer that has already passed the in situ stage, with stromal invasion.

The darker bars (shaded) show the same proportions for an earlier period 1950-51 (where data are available). The proportion of in situ cases increased in each of the hospitals in the ensuing decade, in some instances from zero in 1950-51 to more than 75 per cent in 1960-61.

The above comparison among hospitals is not a precise one, since the proportion of cervical cancer cases that are in situ is strongly influenced by the type of patient seen at each institution. For instance, the more serious and difficult cases may be referred to teaching institutions for diagnosis and therapy, thus increasing the proportion of invasive cases seen in those institutions and decreasing the proportion of invasive cases at the referring hospitals. (Analysis of a sample of case abstracts from one university hospital showed that this was the case: The overall proportion of cervical cancer cases diagnosed while still in situ was 33 per cent. The proportion of in situ cases among those evidently referred to the teaching center was 18 per cent, while the proportion of in situ cases among non-referred cases was about 65 per cent.) That this is not the entire explanation is suggested by the relative positions

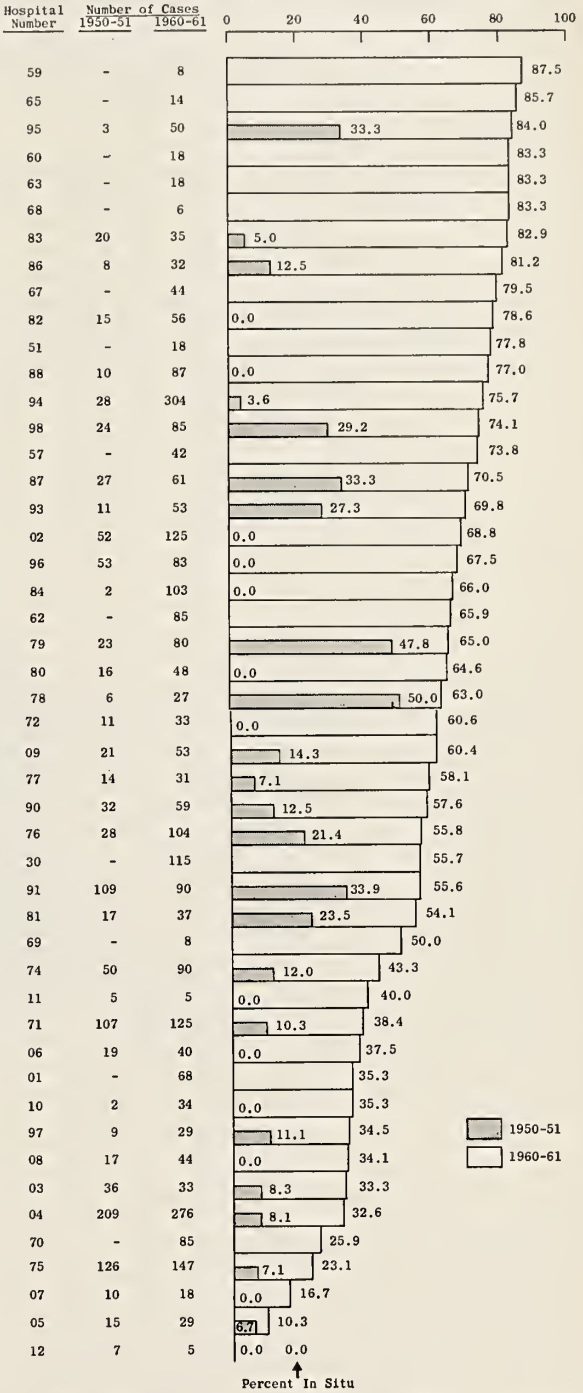


Chart 3.—In Situ Cervical Cancer Cases as a Proportion of Total Cervical Cancer Cases by Hospital and Year Group, California Tumor Registry, 1950-51 and 1960-61.

of a number of large hospitals where members of the gynecological staff probably also care for many referred patients.

As was previously shown in Table 3, the proportion of in situ cases decreases sharply with age, and some types of hospitals deal with an older population than other institutions. Computation of the in situ proportions taking age into account showed some changes in ranking but did not alter the overall relationships.

Considerable variation in the proportion in situ was found even when analysis was restricted to hospitals of similar backgrounds. Each type of hospital—county, community and university—showed a wide range in the proportion of cases in which the lesion was in situ at time of diagnosis.

Whatever the reasons, it is still clear that the populations served by the various institutions differ in the degree to which cytology is used for diagnosis of cervical cancer in an early stage.

REFERENCES

1. American Cancer Society, San Diego County Branch: Papanicolaou smear survey, San Diego County, October 1962.

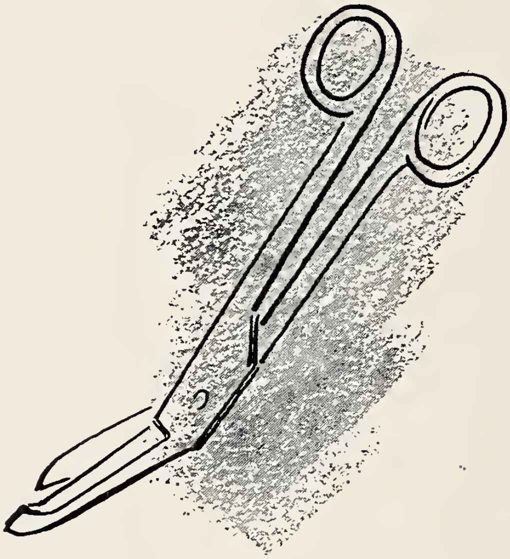
2. Boyes, D. A., Fidler, H. K., and Lock, D. R.: Significance of in situ carcinoma of the uterine cervix, Lancet, 27 January 1962.

3. Breslow, L., and Hochstim, J. R.: Sociocultural aspects of cervical cytology in Alameda County, California, Pub. Health Rep., 79:107, February 1964.

4. Ferber, B., Handy, V. H., Gerhardt, P. R., and Solomon, M.: Cancer in New York State, Exclusive of New York City, 1941-1960, A review of incidence, mortality, probability, and survivorship, New York State Department of Health, 1962.

5. Linden, G., Bragg, K. U., and Breslow, L.: Cancer Registration and Survival in California, California State Department of Public Health, 1963.

6. Ruch, R. M., Blake, C., Abou, A., Lado, M., and Ruch, W. A.: The changing incidence of cervical carcinoma, Am. J. Obst. & Gynec., 89:727, 15 July 1964.



Therapeutic Abortion

Attitudes and Practices of California Physicians

LAWRENCE SHERWIN, A.B., AND EDMUND W. OVERSTREET, M.D., *San Francisco*

■ *A questionnaire about attitudes and practices regarding therapeutic abortion was sent to 943 diplomates of the American Board of Obstetrics and Gynecology listed in California. In the 748 replies received, certain disparities between the views and practices of the specialists on the one hand and current California statutes on the other were noted. The responses to the questions strongly suggested that current California laws governing the performance of therapeutic abortion are in need of modernization and liberalization if they are to accord with the views and practices of California obstetrician-gynecologists.*

A RECENT SPATE of lay publicity has made California physicians particularly aware of the growing controversy about the therapeutic abortion laws of this state. Many are familiar with previous efforts to modernize these laws, and they know that during the past several years bills submitted to the legislature for this purpose have died in committee. This legislative block might well have continued in semi-obscurity but for two recent developments: (1) The rubella epidemic of 1964-1965, and (2) charges of unprofessional conduct preferred by the State Board of Medical Examiners against nine San Francisco physicians for having performed abortions on the indication of maternal first trimester rubella.

Those of us working for liberalization of the law have contended that legislative committees—and California legislators in general—have not been made fully aware of the actual views of the public and of physicians about this matter. A recent sampling poll of California public opinion conducted by the Field Research Corporation indicates that only 25 per cent of the people favor very restrictive abortion laws, while 65 per cent favor liberalizing them.[1] The House of Delegates of the California Medical Association, representing about 22,000 California physicians, passed a resolution at its March 1966 meeting expressing "its belief in the broadening of the therapeutic abortion laws."[2] But specific information about individual attitudes and practices of physicians has been lacking—particularly of the obstetrician-gynecologists who are most directly concerned with the controversy since they perform most of the therapeutic abortions.

Therefore a questionnaire was mailed to 943 diplomates of the American Board of Obstetrics and Gynecology listed at California addresses. Thirty were returned unopened or were invalid because the physicians no longer practiced in California. Valid questionnaires received numbered 748, a return of over 81 per cent of the 913 possible replies. This unusually good response to a questionnaire testifies to the current great concern about the therapeutic abortion prob-

---

From the Department of Obstetrics and Gynecology, University of California, School of Medicine, San Francisco.

Mr. Sherwin is a Student Research Fellow on USPHS Grants Nos. 1-SO1-FR-5355-5 and 5T5-GM-4305.

Submitted 24 August 1966.

Reprint requests to: Department of Obstetrics and Gynecology, University of California School of Medicine, San Francisco 94122 (Dr. Overstreet).

lem among California's obstetrician-gynecologists. Moreover, more than 75 per cent of the returns were signed. (We requested but did not require a signature.)

Attitudes

The first seven items of the questionnaire surveyed the current opinion of these specialists about proper indications for therapeutic abortion. The specific questions and the statistics of the replies are presented in Table 1. Therapeutic abortion on indications covered by the first three questions is legal under present California law, so the large affirmative response would be expected. Indications covered by questions No. 4 through No. 7 are at present not the subject of judicial interpretation in California.

Some physicians have contended that the terminology of proposed revision of the law is dubious, that such terms as "material impairment of maternal health," "material risk" and "significant fetal abnormality" are too vague and unscientific. While it is true that these terms are imprecise and require careful medical judgment for individual definition, the responses to questions No. 4 and No. 5 suggest that they have meaning and are useful to a large majority of specialists.

The replies to question No. 5 are especially important with regard to the current California controversy since the practices among California physicians resulting in charges by the Board of Medical Examiners involved therapeutic abortions for this indication. Hence it is most significant that 77 per cent of the obstetrician-gynecologists who answered expressed belief that this is a valid modern indication for the procedure.

The replies to question No. 6 speak for themselves. The injustice of a law that forces the victim of proved forcible rape or of incest to continue to bear a pregnancy resulting therefrom is recognized by a large proportion in obstetrics and gynecology.

Opponents of proposed liberalized abortion laws have stated that the changes are "designed to allow maximum freedom to do abortions on unwanted pregnancies on socio-economic grounds."[3] The responses to question No. 7 cast a clearer light on this contention. A high proportion of those who answered the questionnaire expressed belief that therapeutic abortion on socio-economic grounds alone is not justified. Clearly there is no majority impetus to legalize elective or "walk-in" abortion.

Personal, Medical or Legal Matter?

About 9 per cent of respondents to the previously mentioned Field Research Corporation poll favored unrestricted abortion.[1] The Supreme Court of the United States has recently affirmed the principle, so far as contraception is concerned, that the personal decision whether or not to conceive children should not be interfered with by written law.[4] Does this principle extend to interruption of early pregnancy? Question No. 8 of our questionnaire assays the opinions of obstetrician-gynecologists on this matter.

	Yes	*No*	*Uncertain*
8. Do you believe that therapeutic abortion is a purely personal and / or medical matter which should *not* be regulated by written law at all?	33.6% (240)	55.3% (395)	11.1% (79)

Practices

The foregoing reports what California specialists were willing to tell us about their attitudes toward therapeutic abortion. How well do their actual practices in this regard conform to their expressed views? For information about this we asked question No. 9:

TABLE 1.—*Questions and Answers on Indications for Therapeutic Abortion*

Questions (Indications)	*Yes*	*No*	*Uncertain*
Do you believe that therapeutic abortion is justified:			
1. For imminent risk of maternal death?	91% (682)*	7% (51)	2% (13)
2. For definite risk of shortened maternal life?	87% (646)	9% (69)	4% (31)
3. For psychiatric certification of suicidal risk?	67% (501)	18% (132)	15% (113)
4. For risk of material impairment of maternal health, physical or mental?	72% (535)	16% (116)	12% (89)
5. For material risk of significant fetal abnormality?	77% (574)	14% (104)	9% (67)
6. For proved forcible rape or incest?	83% (616)	12% (90)	5% (40)
7. For purely socio-economic reasons?	21% (157)	60% (447)	18% (136)

*Per cent quoted is that of total responses to each question; figure in parentheses is actual number of replies; not all questions were answered by all respondents.

TABLE 2.—*Indications on Which Respondents Actually Performed Abortions as Compared with the Indications They Believed Justified Abortion*

*Indication—Question No.**	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Per cent of those (590) who performed therapeutic abortion..	60	68	61	49	64	10	4
Per cent of respondents (748) who feel this indication valid....	91	87	67	72	77	83	21

*The questions are shown in Table 1.

> "For which of the seven indications above have you actually performed therapeutic abortion?"

Only 18 of the 748 specialists left this question unanswered. Of the 730 who did answer it, 590 (81 per cent of the entire 748 respondents) reported having done therapeutic abortion for one or another of the indications. Of the 140 who had never done the procedure, 108 stated that they had no objections to therapeutic abortion but had not had the problem presented.

It is of interest then to examine the physician responses with regard to indications for which they actually performed therapeutic abortions as compared with those they felt to be justifiable. This is set forth in Table 2. This comparison points up some striking aspects of the conflict between current medical thought and practice and California therapeutic abortion statutes. The actual figures for abortions on the current legal indications (numbers 1, 2 and 3) are not particularly significant; the somewhat low performance despite the higher willingness is probably largely explainable by the relatively limited need to perform therapeutic abortion at all. However, despite the dubious legality of indication No. 4, among physicians performing therapeutic abortions 49 per cent translated their own views about it into action. As to indication No. 5, 64 per cent of specialists accepted the legal jeopardy incident to acting on it.

The figures for indication No. 6 are difficult to interpret. The fact that only 10 per cent of specialists who performed abortions had occasion to do so on the grounds of rape or incest does not necessarily bespeak physicians' fear that they may be breaking the law. Not only are such patients few in number but many of them are dealt with on psychiatric grounds under indication No. 3. In any event, this figure would undoubtedly rise materially if indication No. 6 were legalized in accordance with the opinion of 83 per cent of the respondents.

The influence of socio-economic factors on the performance of therapeutic abortion is so subtle a matter that it almost defies analysis. Undoubtedly the sympathies and judgments of physicians are swayed by them. But the performance and the opinion of physicians with regard to indication No. 7 seem to suggest that socio-economic factors *per se* are not of material significance.

REFERENCES

1. San Francisco Chronicle, 26 July 1966.
2. California Medicine, Editorial, 104:409, May 1966.
3. Flanagan, M. B.: Bulletin, San Francisco Medical Society, 39:25, July 1966.
4. Griswold vs. State of Connecticut. 85 Sup. Ct. 1678 381 U.S. 479, July 1965.

Rubella Syndrome

Cardiovascular Manifestations and Surgical Therapy in Infants

DONALD R. SPERLING, M.D., AND JOSEPH J. VERSKA, M.D., *Los Angeles*

■ *Of nine patients under five months of age with cardiovascular manifestations of the rubella syndrome, six had patent ductus arteriosus. Three of these six also had pulmonary artery stenosis. One infant had bilateral isolated pulmonary artery stenosis. The significant clinical findings leading to the diagnosis of pulmonary artery stenosis were axillary murmurs in the presence of right ventricular hypertrophy. Demonstration of a gradient across the stenosis at the time of catheterization, together with cineangiography, established the diagnosis. In two cases ventricular septal defect was the only cardiac anomaly.*

Six babies under five months of age had interruption of a patent ductus arteriosus because of uncontrollable congestive heart failure or failure to thrive. Although growth failure was not necessarily due to heart disease, all were developing satisfactorily following operation.

Diagnosis and therapy of the cardiac complications of the rubella syndrome is possible in the first few months of life. Early recognition of cardiac defects in the young infant with the rubella syndrome permits aggressive medical management and in selected instances surgical therapy.

ATTENTION TO THE cardiovascular manifestations of the rubella syndrome has been given impetus by the nationwide rubella epidemic that occurred in 1964. Recent reports have indicated that, although patent ductus arteriosus is the most common associated cardiac anomaly, pulmonary artery stenosis and other congenital cardiovascular anomalies occur in this syndrome.[3,7] Recently we have seen nine infants with the rubella syndrome in whom cardiovascular anomalies were diagnosed by the age of five months. The purpose of this report is to describe the cardiac manifestations in these infants and to make note that early surgical treatment is indicated in selected instances.

History

The pertinent clinical data are presented in Table 1. Six infants were found to have a patent ductus arteriosus. In three instances there was associated pulmonary artery stenosis. One infant was found to have isolated bilateral pulmonary artery stenosis and in two a diagnosis of ventricular septal defect was made on clinical grounds alone. Three of the infants were premature, weighing 1,644 gm or less at birth. The remaining six ranged from 2,438 gm to 3,714 gm in weight. Five patients had cataracts, bilaterally in three cases. Heart failure occurred in three patients. Five of the six patients who were operated upon had poor weight gain before operation.

From the Department of Pediatrics, University of California, California College of Medicine, Los Angeles 90031, and the Department of Surgery, White Memorial Medical Center, Los Angeles 90033.

Submitted 23 June 1966.

Reprint requests to: Department of Pediatrics, University of California, California College of Medicine, 1721 Griffin Avenue, Los Angeles 90031 (Dr. Sperling).

A history of maternal exposure to rubella in early pregnancy was obtained in seven cases. The two other mothers were not aware of rubella exposure during pregnancy, but their infants had cataracts and proved patent ductus arteriosus, both characteristic of this syndrome. Confirmation by viral isolation was not obtained.

Physical Findings

A systolic thrill was palpable at the left sternal border in seven patients. A cardiac murmur was heard within the first two days of life in three infants, by one month in three infants, and by three and a half months in the remaining three. The most severely affected infant (Case 6, Table 1) had bilateral cataracts, petechiae, viral osteopathy of the long bones, patent ductus arteriosus and pulmonary artery stenosis. He was premature (1,474 gm). A continuous murmur was heard at birth.

Of the infants demonstrated to have patent ductus arteriosus, three had continuous murmurs. The remaining three had systolic murmurs that continued beyond the second sound in the pulmonary area but were not continuous. Two patients who clinically were thought to have small ventricular septal defects had systolic murmurs and thrills at the low left sternal border.

Axillary murmurs were clearly audible in the four patients with pulmonary artery stenosis. Three of these patients had an associated patent ductus arteriosus which was interrupted; however, the axillary murmurs were still heard. Bounding pulses were present in all of the six patients who had patent ductus arteriosus.

Electrocardiographic Findings

Severe right ventricular hypertrophy was noted in the patient with isolated pulmonary artery stenosis (Case 7, Table 1). Of the three patients with both patent ductus arteriosus and pulmonary artery stenosis, one had combined ventricular hypertrophy, one severe right ventricular hypertrophy, and one moderate right ventricular hypertrophy. Both patients with ventricular septal defect had borderline right ventricular hypertrophy. In one of the patients with isolated patent ductus arteriosus the electrocardiogram was considered normal, in another it was interpreted as showing left ventricular hypertrophy, and in the third it was consistent with combined ventricular hypertrophy.

TABLE 1.—*Clinical Data on Nine Patients with Rubella Syndrome*

Case No.	*Sex*	*Birth Date*	*Birth Weight Grams*	*History of Rubella*	*Age Murmur First Heard*	*Heart Failure*	*Cataracts*	*Thrill*	*Wide Pulse Pressure*	*Murmur* *Syst.*	*Dias.*	*Cont.*	*Axil.*	*Diagnosis**
1..........	F	1/ 9/65	3,175	+	1 mo.	—	0	+	+	—	—	3/6	+	PDA (divided) PAS
2..........	F	1/24/65	2,438	—	3½ mo.	+	1	+	+	3/6	1/6	—	—	PDA (ligated)
3..........	F	10/ 1/65	3,714	+	2 mo.	+	0	0	+	3/6	1/6	—	—	PDA (divided)
4..........	F	2/11/65	2,863	—	2 mo.	—	1	+	+	—	—	3/6	—	PDA (divided)
5..........	M	7/20/65	1,503	+	1 mo.	+	0	+	+	3/6	1/6	—	+	PDA (ligated) PAS
6..........	M	11/23/65	1,474	+	Birth	—	2	+	+	—	—	3/6	+	PDA (divided) PAS
7..........	M	2/11/65	2,722	+	¾ mo.	—	2	0	—	2/6	—	—	+	PAS
8..........	F	11/23/65	2,835	+	1 day	—	0	+	—	3/6	—	—	—	VSD
9..........	F	2/23/65	1,644	+	2 days	—	2	+	—	3/6	—	—	—	VSD

*PDA—Patent ductus arteriosus; PAS—Pulmonary artery stenosis; VSD—Ventricular septal defect.

TABLE 2.—*Cardiac Catheterization Data on Seven Patients with Rubella Syndrome*

No. Case	*Age at Time of Study (months)*	*Pressures, mm of Mercury*				*Oxygen Saturation*					*Ductus Entered*
		RV	*MPA*	*RPA*	*Ao*	*SVC*	*RA*	*RV*	*MPA*	*Ao*	
1	4	40/0,5	40/25	19/12	100/50	68	71	64	81	93	Yes
2	4	55/0,5	55/30	–	75/35	–	62	62	81	94	Yes
3	4	30/0,5	30/15	–	100/50	60	61	63	80	–	Yes
4	3	60/0	55/25	–	70/25	71	69	70	82	94	Yes
5	3	60/0,5	60/25	–	100/55	–	70	78	83	90	Yes
6	7 (weeks)	50/0	50/12	20/5	85/40	78	78	80	80	94	Yes
7	2	55/0	45/10	15/5	–	70	74	–	73	95*	–

---

*Left atrial sample; RV—Right ventricle; MPA—Main pulmonary artery; RPA—Right pulmonary artery; Ao—Aorta; SVC—Superior vena cava; RA—Right atrium.

Roentgenographic Findings

Thoracic x-ray films of the patient with isolated pulmonary artery stenosis and of the two with small ventricular septal defects appeared to be normal. In the remaining six patients, pronounced cardiomegaly and increased pulmonary vasculature were demonstrated.

Cardiac Catheterization Findings

The data on seven patients in whom cardiac catheterization and cineangiographic studies were done are shown in Table 2. The ductus was entered from the pulmonary artery in five patients (Figure 1) and in a retrograde fashion from the aorta in another. Increased oxygen saturation in the pulmonary artery over that in the right ventricle was noted in all but one of the patients with patent ductus arteriosus (Case 6, Table 2). Right pulmonary artery stenosis was demonstrated by pull-out pressure recording in three patients, two of whom had associated patent ductus arteriosus. In addition to pressure recording data, pulmonary artery stenosis was demonstrated by cineangiography (Figure 2).

Surgical Intervention

The patent ductus arteriosus was interrupted in six patients before they were five months of age. In three of these infants the indication for operation was uncontrollable congestive heart failure; in the other three, the indications were cardiomegaly, pronounced increase in pulmonary vasculature, and failure to thrive. Only in Case 5 was the ductus found to be less than one-half the diameter of the aorta. In that patient, associated pulmonary artery stenosis was visualized and palpated in the hilum of the left lung. In one patient (Case 2) cardiac arrest occurred when the left lung was retracted to expose the patent ductus. Regular cardiac rhythm was restored immediately. No other operative complications were encountered.

All of the patients in the present series who were operated upon for patent ductus arteriosus have done well during follow-up periods of six to 16

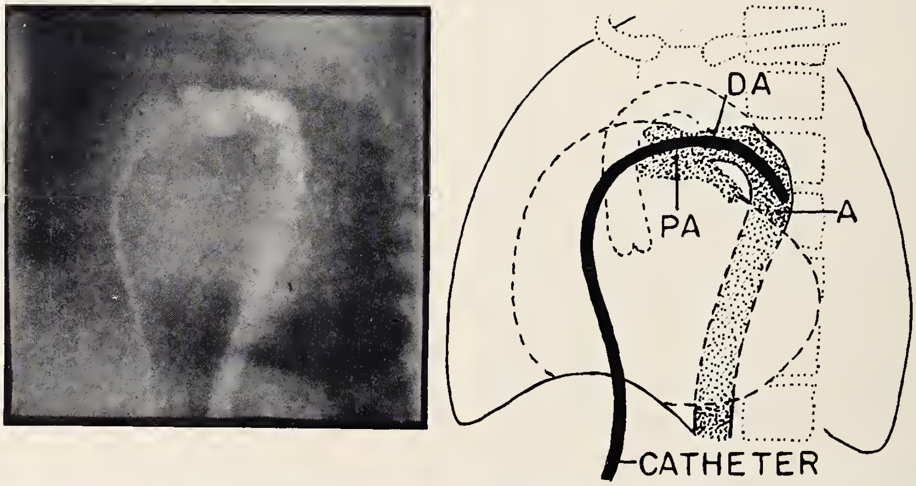


Figure 1.—Left anterior oblique projection. The course of the cardiac catheter is shown passing through the right heart into the pulmonary artery (PA), patent ductus arteriosus (DA), and into the descending thoracic aorta (A).

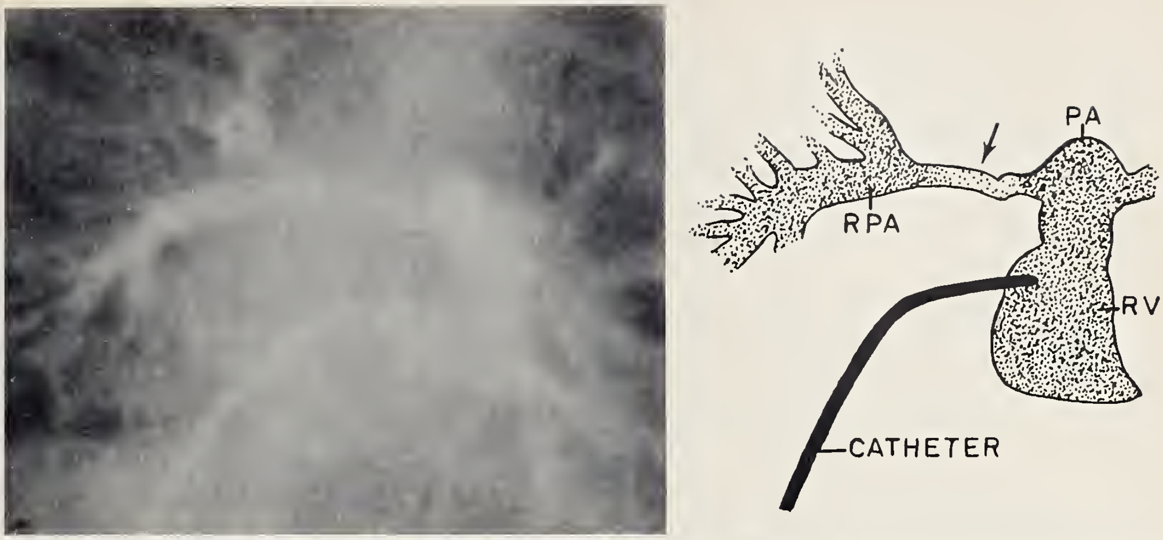


Figure 2.—The right ventricle (RV) and pulmonary artery (PA) are opacified in the AP projection. A narrowing in the right pulmonary artery (RPA) is demonstrated.

months. Heart size returned to normal within six weeks in all but one patient (Case 5) who has associated bilateral pulmonary artery stenosis.

Discussion

In 1941 Gregg[3] made the first observation that maternal rubella in early pregnancy was associated with congenital malformations of the heart. Stuckey[7] reported 27 patients, age three months to 12 years, with a variety of cardiac lesions associated with the rubella syndrome. He indicated that additional cardiac defects would be seen in one-fourth to one-third of the patients with patent ductus arteriosus. A report by Rowe[4] in 1963 helped focus attention on the association of pulmonary artery stenosis with the rubella syndrome. He emphasized the transmission of the murmur to the lateral chest wall as being the major physical finding permitting clinical diagnosis. A more recent communication by Rowe[5] indicates that pulmonary artery stenosis may occur as frequently as patent ductus arteriosus. Our case material confirms the findings of these observers.

In infants under six months of age, cardiac catheterization is recommended even in the presence of a continuous murmur in order to establish the diagnosis of patent ductus arteriosus. This will also serve to assess the presence and severity of other cardiac anomalies. Use of an end-hole catheter entails a possible pitfall in making the diagnosis of pulmonary artery stenosis in the presence of patent ductus arteriosus, since false high pres-

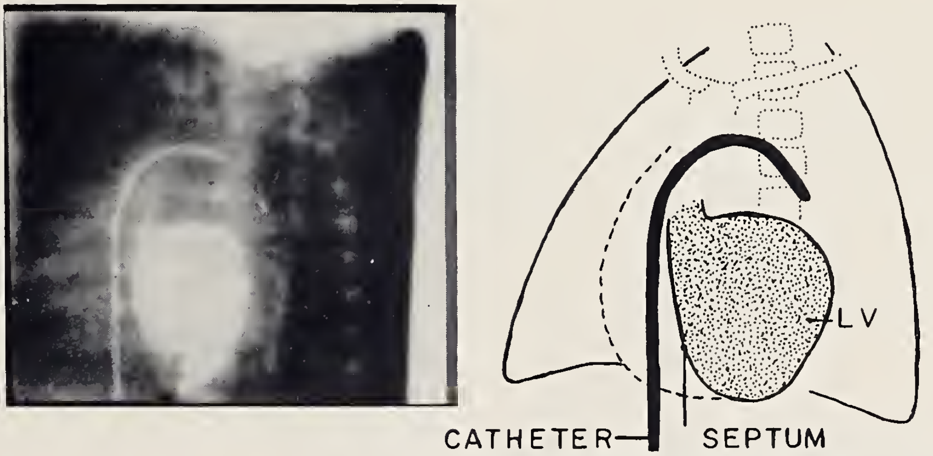


Figure 3.—Left anterior oblique projection, systolic phase. The radiopaque material has circulated through the lungs, left atrium, into the left ventricle (LV). The interventricular septum is demonstrated to be intact.

sure readings at the bifurcation of the pulmonary artery may be obtained when the tip of the catheter is within the ductus itself. An associated ventricular septal defect may also be ruled out by determination of oxygen saturation in each of the right heart chambers and with the use of cineangiography. Figure 3 shows an intact ventricular septum after circulation of radiopaque material into the left ventricle.

Three of the six patients in the present series who were successfuly operated upon for interruption of a patent ductus arteriosus have residual pulmonary artery stenosis with postoperative lateral chest wall murmurs as described by Emmanouilides.[2] These infants, however, have smaller hearts than they had before. They have normal electrocardiograms and they are gaining weight. Interrupting the ductus had duplicate beneficial effects in these patients. The increased pulmonary blood flow was reduced and thereby the flow across the stenotic area was decreased. This lowering of the pressure gradient in turn decreased right heart strain. We believe, therefore, that early interruption of the patent ductus was of particular benefit to these patients.

The patient with isolated bilateral pulmonary artery stenosis had been observed for 14 months at the time of this report. He has normal pulmonary blood flow, and although severe right ventricular hypertrophy continues, as demonstrated by electrocardiogram, he has no other signs of progressive disease. It should be noted, however, that even with such pronounced right ventricular hypertrophy, the right ventricular pressure at cardiac catheterization at two months of age was only 55 mm of mercury. If indicated, an angioplastic procedure with a venous onlay graft as described by Smith[6] can be done to relieve the pulmonary artery obstruction in patients of this kind.

The findings of Rowe and Emmanouilides that pulmonary artery stenosis usually occurs on the right side if it is unilateral was borne out in two of the cases in the present series (Cases 1 and 6). We feel this to be of clinical significance and that it should prompt the physician to auscultate in the right axilla as well as in the usual cardiac areas.

REFERENCES

1. Campbell, M.: Place of maternal rubella in the aetiology of congenital heart disease, Brit. Med. J., 1:691, 11 March 1961.

2. Emmanouilides, G. C., Linde, L. M., Crittenden, I. H.: Pulmonary artery stenosis associated with ductus arteriosus following maternal rubella, Circulation, 29: 514, April 1964.

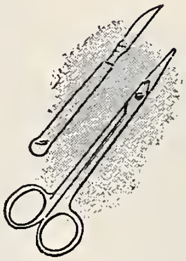
3. Gregg, N. M.: Congenital cataract following German measles in the mother, Trans. Ophthal. Soc. Australia, 3:35, 1941.

4. Rowe, R. D.: Maternal rubella and pulmonary artery stenosis: Report of 11 cases, Pediatrics, 32:180, August 1963.

5. Rowe, R. D.: Cardiovascular lesions in rubella (Letter to the Editor), J. Pediat., 68:147, January 1966.

6. Smith, G. W., Thompson, W. M., Jr., Mueller, W. H., Jr.: Surgical treatment of pulmonary hypertension secondary to multiple bilateral pulmonary arterial stenosis, Circulation (Supplement), 29:152, April 1964.

7. Stuckey, D.: Congenital heart defects following maternal rubella during pregnancy, Brit. Heart J., 18: 519, 1956.



Congenital Anomalies and Viral Infections In Infants

The Etiologic Role of Maternal Viral Infections

HARRY T. WRIGHT, JR., M.D., *Los Angeles*

■ *Some viruses, such as rubella and human cytomegalovirus, are known to cross the placental barrier and infect the fetus. In other cases of maternal viral infections, such as herpes simplex, evidence for transplacental passage is less convincing and fetal damage or neonatal disease may be coincidental or associated with perinatal infection. Certain cases of fetal or neonatal disease following maternal viral infections may be associated with disease in the mother which affects her metabolic processes or the placenta in such a way as to interfere with development of the fetus and infant.*

The possible effects of transplacental viral infections are several. Fetal loss may occur by means of abortion or stillbirth. There may be infection of the fetus, with clinical manifestations such as rash, or without clinical manifestations. The infant may be born with congenital defects, including such deformities as cataracts, cardiac anomalies, mental retardation or cerebral palsy.

Although a number of maternal viral diseases have been etiologically incriminated in congenital defects, only two—rubella and cytomegalovirus infection—are definitely proved to be associated with anomalies or mental retardation in infants.

VIRAL INFECTIONS during pregnancy, Kibrick[14] has said, may be associated with fetal mortality, intrauterine infections, congenital malformations and perinatal disease, as well as with mental retardation and cerebral palsy. Blattner[1] reviewed the etiologic role of viruses in congenital malformations and suggested that viral infections during pregnancy may lead to anomalies.

Certain viral infections in the pregnant host have been transmitted to the fetus. The mechanisms whereby viruses gain access to the fetus are poorly understood; however, it is reasonable to assume that their presence in maternal blood may be one source of infection, and direct extension of virus from the exterior by way of the birth canal may be another.

The presence of certain types of maternal antibody (IgA and IgG, 7S species) in the newborn indicates that certain large molecules can cross the intact placental barrier. Passively acquired

---

From the Department of Pediatrics, University of Southern California School of Medicine, and the Childrens Hospital of Los Angeles.

This investigation was supported by Public Health Service Research Grant No. 5-R01-AI-03079 from the National Institute of Allergy and Infectious Diseases.

On 1 April 1966, this material was presented to the Mental Retardation Institute at Childrens Hospital of Los Angeles as part of the Postgraduate Training Program of the University of Southern California.

Submitted 16 March 1966.

Reprint requests to: Childrens Hospital of Los Angeles, P.O. Box 54700, Terminal Annex, Los Angeles 90054.

antibodies play an essential role in immunity of the neonatal infant but the extent of this profetuses with certain viruses, such as Group B coxsackievirus, rubella and cytomegalovirus, suggests that at least some viruses infecting the mother are capable of crossing the placental barrier. Some of these viruses, such as Group B coxsackievirus and cytomegalovirus, cause little or no illness in the maternal host but severe or fatal disease in the fetus.

Experimental work in which pregnant guinea pigs were inoculated with certain viruses would indicate that the placenta usually acts as an effective barrier against these viral agents.[17] Thus it may be that the transfer of such agents can occur only if there is placental damage.

It would appear that several factors are involved in determining whether or not the fetus will be affected by a maternal infection. The severity of the infection in the mother probably influences the severity of the infection in the fetus or newborn—that is, the more severe the infection in the mother, the more severe will be the infection in the fetus. The type of maternal infection is an important factor; certain viral infections seem to cause a more severe disease in the fetus than they do in the mother. Other infections, which may be severe in the mother, cause only minor clinical manifestations in the fetus or newborn. The length of gestation before infection occurs is also an important factor. It would appear that the fetus would be more severely affected by infection with some viruses early in gestation, whereas infection with other viruses might create a problem regardless of when the mother became infected.

There are adequate data indicating that newborn babies produce viral antibodies under certain conditions but sometimes engender no such response. Protection from disease may or may not be accompanied by the presence of antibodies. Not all the factors that enter into this complex situation are known, but it would appear that immunity involves more than the presence or development of antibodies.[6]

Over a dozen viral diseases occurring during pregnancy may be associated with untoward effects on the fetus or newborn. However, only two maternal viral infections, rubella and cytomegalovirus infection, have been associated definitely with an increased risk of anomalies in infants. Other observed anomalies in infants following maternal viral disease could be coincidental. Certain observed effects on the fetus following these diseases in the mother have been described.

Rubella (German Measles)

The true nature and potential severity of rubella infection in the expectant mother became apparent in 1941 when Gregg,[10] an Australian ophthalmologist, first reported the relationship between rubella in the pregnant woman and the occurrence of congenital malformations in her offspring. The most common abnormalities encountered in children whose mothers had this disease early in gestation include congenital cataract, congenital heart disease, especially patent ductus arteriosus, perception deafness, microcephaly and mental deficiency. Less frequently seen are other conditions such as microphthalmus, buphthalmos, retinal lesions, talipes equinovarus, syndactyly, hypospadias, generalized muscular weakness, cerebral diplegia, cleft palate and dental anomalies. These have been called the rubella syndrome.

In some studies, 50 per cent or more of infants born to women who had rubella during the first four weeks of pregnancy have had severe congenital anomalies. If exposure occurs during the second or third trimester, there is much less risk of the rubella syndrome resulting. However, during the recent rubella epidemic the occurrence of persistent infection in the fetus has been reported when the mother contracted rubella in the second trimester. In such circumstances, the infant may shed rubella virus for many months after birth.

DeKaban and associates[4] showed that the highest incidence of five major abnormalities—cataract, congenital heart disease, deafness, microcephaly and mental retardation—results when rubella infection occurs in the first five weeks of gestation.

In 1962 the cultivation of rubella virus in tissue culture by Weller and Neva[28] and Parkman and associates[21] made it possible to carry out virus isolation and serological studies of patients with typical, atypical and subclinical types of rubella. Studies of the nation-wide epidemic of rubella in 1964 have clarified our understanding of the pathogenesis of congenital rubella.

If viremia occurs during pregnancy, the fetus under 12 weeks of age is particularly susceptible to infection, which persists and is present at birth. Clinical manifestations include: (1) Low birth weight; (2) eye lesions, i.e., cataract, glaucoma, retinitis; (3) deafness; (4) brain lesions associated with microcephaly, meningoencephalitis, hydrocephalus and mental retardation; (5) cardiac defects, i.e., patent ductus arteriosus, ventricular septal defect; (6) thrombocytopenia purpura; (7) hepatosplenomegaly; (8) pneumonitis; (9) jaundice; and (10) bone lesions. Since infants with congenital rubella infection may shed virus from the throat and urine for at least six months after birth, they may spread disease.[16]

In 1958, studies by Krugman and Ward[15] showed that neutralizing antibody to the virus of rubella was present in ordinary gamma globulin; they suggested the relative efficacy of these preparations in the prevention of clinical manifestations of the disease. More recent studies by Krugman[16] and others have yielded information showing less definite effects from the use of gamma globulin. The question of therapeutic abortion in women who develop clinical rubella during pregnancy invariably arises. The decision must be based on many factors and in each case weighed individually. Recent studies have indicated that human gamma globulin may suppress the clinical manifestations of rubella in the mother without preventing the occurrence of viremia. Studies to determine whether gamma globulin does or does not reduce the risk of congenital malformations, stillbirths or abortions are in progress by Dr. John Sever of the National Institutes of Health.

Cytomegalic Inclusion Disease

The clinical entity referred to as cytomegalic inclusion disease, or generalized salivary-gland virus disease, has become a more familiar problem within the past decade since exfoliative cytologic studies and techniques for isolation of the causative virus have resulted in the recognition of cases during life. Human cytomegalovirus appears to produce no demonstrable illness in the mother, yet may give rise to severe, frequently fatal disease in the fetus and newborn.[32]

In retrospect, a stillborn with inclusion-bearing cells in the liver, lung and kidney reported by Jesionek in 1904 probably represents the first example of generalized cytomegalic inclusion disease.[11]

The distinctive morphologic feature of cytomegalic inclusion disease is the large inclusion-bearing cell, which may appear in almost any organ. The large intranuclear inclusion is surrounded by a clear halo, which separates it from a distinct nuclear membrane. A cytoplasmic or paranuclear inclusion may be found frequently in infected cells.

In 1953, Fetterman[8] detected the inclusion-bearing cells in urinary sediment, thereby introducing exfoliative cytology as a diagnostic procedure; and in 1956 Smith,[24] Rowe[22] and Weller[26] isolated the virus from the urine, salivary gland, adenoid tissue and liver of infected infants, introducing viral isolation techniques for diagnosis.

The clinical manifestations regularly observed in patients with this disease are most clearly defined as they appear in the newborn, premature infant. Prominent features in the typical cases include jaundice, hepatosplenomegaly, petechiae and microcephaly as well as the laboratory findings of anemia, hyperbilirubinemia, thrombocytopenia, paraventricular intracerebral calcifications, inclusion-bearing cells in the urine and the presence of virus in the urine and throat swabbings. These findings in 12 infants infected with human cytomegalovirus were summarized by Wright and associates,[32] who emphasized that infection with these agents in utero or in the neonatal period is not necessarily fatal.

The sequelae of such infections may range from recovery to varying degrees of neurologic involvement, including hydrocephalus, microcephaly and cerebral calcifications, usually in association with motor impairment and mental retardation. However in only three of seven patients tested in one series was retardation considered severe at one year of age.[32] The persistence of hepatosplenomegaly and the variety of tissues in which inclusions have been found suggest that the sequelae of this disease may not necessarily be limited to the central nervous system. In some cases, the clinical histories resembled those of neonatal hepatitis, and virus has been grown from the liver in such cases.[27]

A long-term evaluation of the physical and mental development is needed to define the prolonged effects of congenital infection with human cytomegalovirus. Such a study is under way in several centers.

Other Viral Diseases Possibly Associated With Anomalies

Herpes Simplex

The primary infection with herpes simplex usually occurs between six months and three years of age. Infection with herpes simplex virus is extremely common in older children and adults and is usually inapparent or associated with a vesicular infection of the skin or mucous membranes. However, if newborn infants should become infected with this agent, a severe disseminated disease characterized by extensive infection of many organs, primarily the liver, lungs and adrenal glands, occurs within the first week of life and usually results in death.[31]

Infants with this disease have fever, profound weakness, skin vesicles, jaundice, hepatosplenomegaly, ulceration of the esophagus, dyspnea, cyanosis and bleeding tendencies associated with thrombocytopenia.[23,31]

Pathologically, affected organs are riddled with pale, yellow, firm, necrotic nodules measuring a few millimeters in diameter. Characteristic inclusion-bearing cells (Cowdry Type A) may be seen microscopically in the infected organs.

Transmission of infection from the mother to the infant most frequently occurs during passage through the birth canal or by contact after birth, but transplacental infection also is known to occur.[23]

Generalized disease in the newborn infant due to herpes simplex virus is so rarely encountered and has so wide a spectrum of clinical manifestations that this diagnosis is usually not considered, even in infants with severe disease.

For the infants who recover the prognosis is poor. Chorioretinitis and blindness as well as severe mental and psychomotor retardation are the rule in surviving infants with this disease.

Although rare, generalized herpes simplex should be considered in severe illness of the newborn when symptoms suggest an infectious disease.

Coxsackievirus Group B Infections

Coxsackieviruses Group B types one to five have been established as etiologic agents of severe, often fatal illness in newborn infants in which there is encephalitis and extensive focal myocarditis.[30] The liver, pancreas, adrenal glands and other abdominal organs may also be affected. The mother may have had a pleurodynia-like illness late in pregnancy and this, along with early signs of clinical illness in the infant, suggests intrauterine infection.

The clinical manifestations include a biphasic course, feeding difficulty, respiratory distress, lethargy, cyanosis, hepatomegaly and jaundice. Collapse and death may occur within a few days, or apparent recovery may occur over the succeeding few weeks. Myocarditis has been the most constant pathologic finding, although meningoencephalitis and hepatic necrosis are also frequently observed postmortem.[9]

Known cases of this disease in newborns may be divided into two groups. Infants may have extremely severe and generalized disease associated primarily with myocarditis, encephalitis, vascular collapse and death, or they may have minor illnesses, such as aseptic meningitis, and recover. The data on long-term follow-up of such patients is scanty, and it is possible that certain cases of chronic myocarditis or mental retardation appearing in later life are sequelae of early infection with group B coxsackievirus.[14]

Rubeola

There are several recorded cases in which maternal measles has been followed by the birth of defective children. The observed malformations have included mental retardation, congenital heart disease, deafness, cleft lip, talipes equinovarus and genu valgum. Since virus was not isolated in those cases, the possibility exists that infection with rubella may have been a factor, or they may have occurred by chance. Packer[20] showed that when measles was present at birth, the disease was usually in the same stage in the infant as it was in the mother. This suggests that the virus of measles can cross the placenta at any stage of gestation.

Mumps

Evidence has been accumulating for a number of years that infection with the virus of mumps occurring in early pregnancy can affect the fetus adversely; spontaneous abortion and stillbirth have been reported.[1] Congenital defects described following maternal mumps include spina bifida occulta, urogenital tract deformity, external ear anomalies, hypospadias, heart lesions and meningoencephalitis. These defects may have occurred by chance. Apparently no case of mental retardation following maternal mumps has attracted attention.

Varicella and Herpes Zoster

Although varicella is frequently transferred from a mother with the disease to the fetus in utero, no case of congenital defect or mental retardation in the infant has been reported. Varicella has been present at birth or has occurred as late as the tenth day of life when the mother has the disease at the time of delivery. In fatal cases of congenital or early neonatal varicella, postmortem examination has revealed a generalized widespread infection with focal areas of necrosis and hemorrhage in many organs.[1] Duehr[5] described congenital cataracts in two patients whose mothers had herpes zoster (a virus which is considered identical to the chickenpox virus) within the first trimester of pregnancy. Other anomalies included mental retardation, microphthalmus and talipes equinovarus. It is interesting that these anomalies are similar to those produced by rubella.

Smallpox

The virus of smallpox crosses the placenta and thus may be the cause of disease in the fetus while in utero, or following birth if the disease is still active in the mother.[18] Spontaneous abortion is common because of the severity of the disease in the mother. Rarely the infant may be born with clinical evidence of the disease or with congenital malformation such as cataract or hydrops fetalis. No report of mental retardation has come to my attention.

Hepatitis

Stokes and coworkers[25] presented evidence that neonatal hepatitis could be associated with transmission of virus across the placenta. In some cases, consideration of the incubation period pointed to intrauterine infection, and in one case the presence of virus was demonstrated by the inoculation of mother's and infant's blood into human volunteers, disease resulting. The relatively low incidence of infectious hepatitis in pregnancy has made it difficult to obtain accurate data concerning the effect of these agents upon the fetus. In 1951 Kass[12] described a decidedly hydrocephalic and microphthalmic infant whose mother had had infectious hepatitis in the second and third months of pregnancy, and Blattner[1] reported the case of an infant (observed by Hellbrügge) born to a mother who had had hepatitis during her fifth week of pregnancy; this infant showed signs of physical and mental retardation at three months of age, as well as eye disease involving the iris, choroid and optic nerve.

Influenza

The various forms of influenza are often severe in pregnant women and the incidence of abortion, stillbirth and premature birth has been considered high during epidemics. Kaye and associates,[13] in a review of congenital anomalies over a five-year period in Chicago, noted three infants with multiple defects and mental retardation whose mothers in their first trimester had had an illness described as severe influenza, due to "Virus-X," with high fever. A more recent study prompted by the appearance of Asian influenza in California indicated there was no significant difference in incidence of anomalies in infants whether the mothers had or had not been infected during pregnancy.[29] Two infants whose mothers had been infected were anencephalic, however.

Arthropod-Borne Encephalitides

Eichenwald and Shinefield[6] pointed out that of the arthropod-borne (Arboviruses) encephalitides, western equine encephalomyelitis (WEE) and eastern equine encephalomyelitis (EEE), are the only two types of this infection of clinical importance during the newborn period in the Northern Hemisphere. Infection with viruses causing St. Louis encephalitis and Japanese B encephalitis is virtually nonexistent during the neonatal period. Newborn infants may acquire WEE by the transplacental transmission of the agent or be infected by the bite of infected mosquitoes. Many of the manifestations of central nervous system damage caused by this virus, such as seizures, motor impairment and mental retardation, may not become clinically apparent until some months after the initial infection.

Other Viral, or Suspected Viral, Infections

Spontaneous abortion, stillbirth, premature delivery and congenital infection have been commonly associated with poliomyelitis during pregnancy. Bowers and Danforth[2] followed the course of 24 full-term infants whose mothers had poliomyelitis during pregnancy and presented data suggesting these babies showed a significant retardation in general development and birth weight.

The cause of infectious mononucleosis is unknown but is suspected to be viral. Cases of infectious mononucleosis have been known to occur during pregnancy, and newborn infants of the affected mothers have been observed and followed, but no definite evidence suggesting mental abnormalities in these children has been reported.[1]

Day[3] and other investigators have suggested "clustering"—that is, increased incidence in time and space—of certain diseases due to chromosomal abnormalities, such as mongolism. Nichols[19] has shown that certain viruses can produce several changes in chromosomes. It is not known at present whether there is any association between maternal viral disease and chromosomal abnormality in the offspring.

Prevention of Viral Diseases

The scope of this report is too limited for an extensive discussion of preventive measures for viral diseases. Chemical substances known to have some antiviral activity might be considered useful if begun soon after birth; however, associated side effects might rule them out. One of the halogenated pyrimidines, IDU (5-iodo-2′-deoxyuridine), may become useful in the systemic treatment of congenital herpes simplex or cytomegalovirus infections, both of which are desoxyribonucleic acid viruses and cause severe disease and mental retardation; however, subsequent dangers due to the use of such a drug might be so great as to prevent its use. Evidence has recently been presented which indicates this substance becomes incorporated in cellular DNA, causing a sensitization to ultraviolet light and x-ray, and hence might theoretically lead to mutations of possible oncogenic nature.[7]

The practicality and success of the immunological approach to the control of viral diseases may be exemplified by the remarkable reduction in the incidence of smallpox and poliomyelitis since widespread use of specific antiviral vaccine. Since infants may be born with clinical viral disease or the mother might have had a viral disease for which no vaccine is available, the immunological approach is not appropriate in all situations.

The use of gamma globulin in the newborn when a viral disease is present or suspected is controversial. Use of it in diseases such as generalized herpes simplex, hepatitis and varicella has been suggested, but whether it can prevent resulting complications such as mental retardation is not known.

REFERENCES

1. Blattner, R. J., and Heys, F. M.: Role of viruses in the etiology of congenital malformations; From Progress in Medical Virology, Vol. 3, Edited by E. Berger and J. L. Melnick, Hafner Publishing Company, Inc., New York, 1961, pp. 311-362.

2. Bowers, V. H., Jr., and Danforth, D. N.: The significance of poliomyelitis during pregnancy, Am. J. Obst. and Gynec., 65:34-39, January 1953.

3. Day, Robert W.: The epidemiology of chromosome aberrations, Am. J. Human Genetics, 18:70-80, January 1966.

4. DeKaban, A. S., O'Rourke, J., and Cornman, T.: Abnormalities in offspring related to maternal rubella during pregnancy, Neurology, 8:387-392, May 1958.

5. Duehr, P. A.: Herpes zoster as a cause of congenital cataract, Am. J. Ophthal., 39:157-161, February 1955.

6. Eichenwald, H. F., and Shinefield, H. R.: Viral infections of the fetus, premature and newborn infant, Advances in Pediatrics, 12:249-306, 1962.

7. Erikson, R. L., and Syjbalski, W.: Molecular radiobiology of human cell lines. III. Radiation-sensitizing properties of 5-iododeoxyuridine, Cancer Res., 23:122-130, January 1963.

8. Fetterman, George H.: A new laboratory aid in the clinical diagnosis of inclusion disease of infancy, Am. J. Clin. Path., 22:424-425, May 1952.

9. Gear, James H. S.: Coxsackie virus infections of the newborn; From Progress in Medical Virology, Vol. 1, Edited by E. Berger and J. L. Melnick, S. Karger, Basel/New York, 1958, pp. 106-121.

10. Gregg, N. M.: Congenital cataract following German measles in the mother, Tr. Ophth. Soc. Australia, 3:35-46, 1941. Quoted by Blattner, R. J., in Ref. #2.

11. Jesionek and Kiolemenoglou: Übereinen Befund von protozoenartigen Gebilden in den Organen eines Feten, Münch. med. Wschr., 51:1905-1907, 1904.

12. Kass, A.: Congenital hydrocephalus in a newborn infant: Epidemic hepatitis in the mother in the 2nd and 3rd month of pregnancy, Acta Paed., 40:239-248, May 1951.

13. Kaye, B. M., Rosner, D. G., and Stein, I. F.: Viral diseases in pregnancy and their effect upon the embryo and fetus, Am. J. Obst. and Gynec., 65:109-119, January 1953.

14. Kibrick, Sidney: Viral infections of the fetus and newborn; From Perspectives in Virology, Vol. II, Edited by M. Pollard, Burgess Publishing Company, Minneapolis, 1961, pp. 140-159.

15. Krugman, S., and Ward, R.: Rubella: Demonstration of neutralizing antibody in gamma globulin and re-evaluation of the rubella problem, New Engl. J. Med., 259:16-19, 3 July 1958.

16. Krugman, Saul: Rubella—New light on an old disease, J. Pediat., 67:159-161, August 1965.

17. Markham, F. S., and Hudson, N. P.: Susceptibility of the guinea pig fetus to the submaxillary gland virus of guinea pigs, Amer. J. Path., 12:175-182, March 1936.

18. Marsden, J. P., and Greenfield, C. R. M.: Inherited smallpox, Arch. Dis. Child., 9:309-314, October 1934.

19. Nichols, Warren W.: The role of viruses in the etiology of chromosomal abnormalities, Am. J. Human Genetics, 18:81-92, January 1966.

20. Packer, A. D.: The influence of maternal measles on the unborn child, Med. J. Aust., 1:835-838, 24 June 1950.

21. Parkman, P. D., Buescher, E. L., and Artenstein, M. S.: Recovery of rubella virus from army recruits, Proc. Soc. Exper. Biol. Med., 111:225-230, October 1962.

22. Rowe, W. P., Hartley, J. W., Waterman, S., Turner, H. C., and Huebner, R. J.: Cytopathogenic agent resembling human salivary gland virus recovered from tissue cultures of human adenoids, Proc. Soc. Exper. Biol. Med., 92:418-424, June 1956.

23. Schaffer, Alexander J.: Infections caused by filterable viruses: Generalized herpes simplex; From Diseases of the Newborn, 2nd Edition, W. B. Saunders Company, Philadelphia-London, 1965, pp. 732-734.

24. Smith, Margaret G.: Propagation in tissue cultures of cytopathogenic virus from human salivary gland virus (SGV) disease, Proc. Soc. Exper. Biol. Med., 92: 424-430, June 1956.

25. Stokes, J., Jr., Wolman, I. J., Blanchard, M. C., and Farquhar, J. D.: Viral hepatitis in the newborn: Clinical features, epidemiology and pathology, Am. J. Dis. Child., 82:213-216, August 1951.

26. Weller, T. H., Macaulay, J. C., Craig, J. M., and Wirth, P.: Isolation of intranuclear inclusion producing agents from infants with illness resembling cytomegalic inclusion disease, Proc. Soc. Exper. Biol. Med., 94:4-12, January 1957.

27. Weller, T. H., and Hanshaw, J. B.: Virological and clinical observations on cytomegalic inclusion disease, New Engl. J. Med., 266:1233-1244, 14 June 1962.

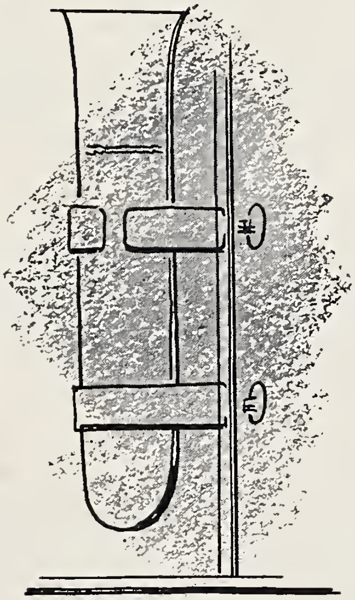
28. Weller, T. H., and Neva, F. A.: Propagation in tissue culture of cytopathic agents from patients with rubella-like illness, Proc. Soc. Exper. Biol. Med., 111: 215-225, October 1962.

29. Wilson, M. G., Heins, H. L., Imagawa, D. T., and Adams, J. L.: Teratogenic effects of Asian influenza, J.A.M.A., 171:638-641, 10 October 1959.

30. Wright, H. T., Jr., Okuyama, K., and McAllister, R. M.: An infant fatality associated with Coxsackie B virus, J. Pediat., 63:428-431, September 1963.

31. Wright, H. T., Jr., and Miller, A.: Fatal infection in a newborn infant due to herpes simplex virus, J. Pediat., 67:130-132, July 1965.

32. Wright, H. T., Jr., Goodheart, C. R., Koch, R., and McAllister, R. M.: Human cytomegalovirus: Clinical and laboratory studies of infected infants. In manuscript.



Cardiac Valve Replacement in Patients Over Sixty

A Report of Ten Operations with One Death

BENSON B. ROE, M.D., AND JOHN C. HUTCHINSON, M.D.,
San Francisco

■ *Of 85 patients who underwent cardiac valve replacement, 10 were 60 or more years old. Nine of the 10 lived, and the excellent results confirmed that advanced age does not contraindicate major corrective operations.*

MAJOR SURGICAL procedures are believed to be more dangerous in elderly patients since cardiopulmonary reserve tends to decrease progressively with age. It would be reasonable to assume, therefore, that open-heart operations in older patients would be associated with prohibitive mortality.[7] Our recent experience suggests, however, that persons in the seventh decade of life can tolerate major cardiac procedures with good results if appropriate precautions are taken.

Clinical Material

This report presents the results of operation in five male and five female patients 60 or more years old who were part of a total series of 85 patients with cardiac valve replacement. A cardiac valve was replaced in all ten patients and in two of the patients an additional corrective procedure was performed on another valve. Because of the limited life expectancy in this age group and the anticipated higher operative risk, every patient accepted for operation had Class III or IV cardiac dysfunction and was in danger of dying unless the condition of the heart could be improved by mechanical correction. Coronary artery disease, renal impairment, pulmonary disease or other factors which might increase the surgical risk were not regarded as contraindications to operation.

Methods

Perfusion. Total body perfusion was required for 61 to 182 minutes at flow rates ranging from 1.8 to 2.7 liters per square meter of body surface per minute, with moderate hypothermia (25°C). A disposable bubble bag oxygenator* primed with modified Ringer's solution was used. Deliberate hemodilution to a mixed hematocrit of 22

From the Departments of Surgery and Medicine, University of California School of Medicine, San Francisco.

Submitted 30 March 1966.

Reprint requests to: Department of Surgery, U.C. School of Medicine, San Francisco 94122 (Dr. Roe).

*Manufactured by Travenol Laboratories, Morton Grove, Illinois.

TABLE 1.—*Clinical Data on Ten Cases*

Case No.	Age and Sex	Diagnosis	Cardiac Class	Significant Catheterization	Valve Replaced
1	65 F	Mitral stenosis; mitral insufficiency; tricuspid insufficiency; pulmonary emboli	III-IV	Cardiac index 2.6 Left atrium 33 Pulmonary artery 68/32, $\overline{44}$	Mitral
2	61 M	Mitral stenosis; mitral insufficiency; tricuspid insufficiency; commissurotomy 1960	IV	Cardiac index 2.3 Left atrium 32 Pulmonary artery 80/35, $\overline{52}$	Mitral; tricuspid annuloplasty
3	60 M	Aortic stenosis; aortic insufficiency; mitral stenosis	III	Cardiac index 1.6 Left atrium 25	Aortic; mitral commissurotomy
4	62 M	Acute aortic insufficiency; bacterial endocarditis; mycotic embolus; obstructive airway disease	IV	Left atrium 23 Right ventricle 60/2	Aortic (Magovern)
5	63 M	Aortic stenosis; aortic insufficiency; myocardial infarct	III	Cardiac index 2.6 Left atrium 22 Pulmonary vascular resistance 2	Aortic
6	70 F	Luetic aortic insufficiency	III	None	Aortic
7	65 F	Severe aortic stenosis; angina; renal tuberculosis; nephrectomy	III angina	Aortic gradient 150 Left atrium 17	Aortic
8	64 M	Aortic stenosis; angina; obstructive airway disease	III angina	Aortic gradient 300 Cardiac index 1.8 Left atrium 30 Right ventricle 87/12	Aortic
9	65 F	Mitral insufficiency; atrial septal defect	III	None	Mitral
10	60 F	Mitral stenosis; mitral insufficiency; commissurotomy 1957; pulmonary emboli	IV	Cardiac index 2.7 Left atrium 27	Mitral

TABLE 1.—*Additional Clinical Data on Ten Cases*

Case No.	Bypass Time (minutes)	Postoperative Complications	Hospital Days	Follow-Up Data	Follow-Up Period (months)
1	103	Pulmonary embolus and myocardial infarction	32	Alive; Class I-II	14
2	182	Oliguria for two days	17	Alive; resistant atrial fibrillation; Class II	10
3	138	None	16	Alive; cardioversion; Class I-II	....
4	61	Metabolic alkalosis; stress ulcer; staphylococcus bronchitis	36	Alive; Class I-II	7
5	140	Arrhythmias; stress ulcer	25	Alive; Class II; slight aortic insufficiency	5
6	105	Low serum potassium; ventricular tachycardia and fibrillation	13	Alive; Class I	3
7	116	Died in operating room; right coronary artery not perfused	0	Died	17
8	128	Hematoma left groin	21	Alive, Class II; cardioversion	16
9	110	Brief ventricular fibrillation	11	Alive, Class I	16
10	108	None	10	Alive; cardioversion	15

to 26 resulted in apparently satisfactory perfusion as judged by: (1) Rare and minimal base deficit (metabolic acidosis); (2) increased urinary output during and after perfusion; and (3) prompt recovery of consciousness.

Technique. Valve replacement was done with the standard operative technique. The Starr-Edwards ball-valve prosthesis was used for both mitral and aortic replacement with the exception of Case 4 (Table 1). This patient had active bacterial endocarditis, and a Magovern sutureless valve was used to avoid a cloth cuff. Every patient but one (Case 7) had constant coronary perfusion throughout the intracardiac procedure. When aortic cross-clamping was required, self-retaining cannulas[6] were inserted in both coronary ostia for uninterrupted perfusion through a separate pump at 150 to 250 ml per minute, except in Case 9 where intermittent coronary perfusion was obtained by interrupted aortic cross-clamping with hypothermic protection (24.5°C).

Critical Periods

The management of this marginally compensated group is necessarily more demanding and precise than that of younger and less critically ill patients. The critical periods are: (1) During restoration of cardiac function and resumption of circulatory load; and (2) the postoperative period of 24 to 72 hours when myocardial dysfunction, distorted hemodynamics, impaired pulmonary function, fluid shifts, renal dysfunction and altered electrolyte patterns are present.

Operative Management

The first danger period begins with completion of the intracardiac procedure, when the heart is filled and defibrillated. Meticulous prevention of air embolism and ventricular distension is necessary since these phenomena may occur so quickly that they pass unrecognized. Goldfarb and Bahnson[2] demonstrated in dogs that an air embolus of only 0.1 ml will significantly impair myocardial function. We routinely vent the high point of the ascending aorta with a special needle similar to that described by Groves and Effler[3] and are frequently astonished by the number of bubbles that appear after supposedly careful filling of the heart.

Ventricular distension, usually caused by an incompetent aortic valve or prosthesis, or by a jammed ball resisting ventricular outflow, can result in prolonged or fatal impairment of ventricular function. To prevent this, a large-bore decompression tube should be maintained in the left ventricle until the critical period is past.

At the end of by-pass, restoration of circulating volume (adequate to drive an impaired ventricle) can be safely accomplished only with the help of left atrial pressure measurements. Experience has abundantly demonstrated the inadequacy of empirical blood replacement,. since the heart with a low output may be fatally overloaded during an attempt to restore normal systemic arterial pressure. Conversely, normal blood volume may be inadequate to provide the elevated left atrial pressures which are frequently necessary to achieve maximum left ventricular output.

A weakly contracting heart may have a dramatic inotropic response to the administration of calcium ion or isoproterenol. Although these drugs may be needed only temporarily, they may be indispensable in restoring adequate coronary (and central) circulation, and in preventing progressive acidosis and ischemic fibrillation. They must be kept in readiness during this phase of the procedure.

Postoperative Management

During the second critical period immediately following operation, other potential dangers must be recognized and avoided.

Deficient Cardiac Output. Hypovolemia and impaired myocardial function are both potential postoperative problems and have indistinguishable clinical manifestations. Myocardial performance is temporarily depressed in many patients undergoing valve replacement and the heart may be driven into irreversible failure when blood is given to raise the arterial pressure. On the other hand, excessive caution in the postoperative replacement of blood (particularly when blood loss is unrecognized or miscalculated) may result in fatal shock. To avoid this dilemma and to guide postoperative blood administration precisely, left atrial pressure is monitored through a fine polyvinyl catheter brought out through the skin, as suggested by Kirklin and Theye.[4]

Inotropic Drugs. When depressed myocardial performance results in a progressive circulatory deficit, survival depends upon augmenting performance by inotropic drugs, by reducing metabolic needs, or both. We use a constant infusion of diluted isoproterenol for this purpose because it has no undesirable vasoconstrictor effects, but occasionally patients will respond more satisfactorily to epinephrine.[5] Efficacy of the inotropic drug is easily demonstrated by the rise in left atrial pressure, drop in systemic pressure, metabolic acidosis and oliguria that occur when the drug is temporarily discontinued during the low output period.

Ventilatory Insufficiency. Hypoxia has been emphasized as a postoperative hazard in open-heart operations, and the need for assisted ventilation during this period is obvious. We have learned, however, that the patient's color is an unreliable indication of hypoxia. Frequent analysis of blood gas can be performed on samples withdrawn from the intra-arterial cannula used to monitor pressure. In most patients some degree of atelectasis develops, with pulmonary shunting and arterial desaturation for several hours postoperatively even when the pleural spaces remain intact. During this time the patient may have adequate alveolar ventilation (normal arterial pCO_2) without clinical cyanosis, but with significant hypoxemia. He may become insidiously acidotic without a constant high oxygen atmosphere and assisted ventilation, and "unexplained" ventricular fibrillation may develop.

Ventricular Fibrillation. In two patients serious arrhythmias and ventricular fibrillation developed, requiring prompt electrical depolarization. In Case 6 frequent extrasystoles led to fibrillation three times and remained a hazard until hypokalemia (3.0 mEq per liter) was corrected. Normal preoperative serum potassium and the 5 mEq of potassium present in the priming solution were inadequate to prevent hypokalemia. The patient would have died if this had not been recognized. Postperfusion hypokalemia occurred frequently in our series and is discussed in recently published reports.[1]

Results

Nine patients survived and all were improved to at least Class II; none had serious complications or lasting residual defects (Table 1). No thromboembolic complications, or hemorrhagic complications from anticoagulation, have occurred so far.

The one patient who died in this series was a 65-year-old woman (Case 7) with severe aortic stenosis complicated by angina pectoris at rest. A stenotic but patent right coronary ostium was seen on the angiocardiogram. During operation the ostium was gently dilated but attempts to perfuse it were unsuccessful. After the valve was replaced the ventricles could not be defibrillated. At autopsy an arteriosclerotic plaque was found to be separated from its base and acting as a flap valve at the origin of the right coronary artery. In retrospect this patient might have been saved if a suitable onlay graft had been used to enlarge the right coronary ostium at the outset of the procedure.

Discussion

This experience demonstrates that the potential hazards of prolonged and complicated intracardiac procedures can be avoided even in elderly patients. The mortality rate of 10 per cent in this series is comparable with that of 16 per cent in 75 younger patients who had single and multiple valve replacements during the same period. Our more recent experience of 2 per cent mortality in 46 consecutive patients of all ages further supports a more liberal attitude toward operation in the older patients.

Recognition and management of the cardiopulmonary problems associated with these operations are dependent upon attention to important details, particularly in aged patients.

Micro-air embolism is common and difficult to avoid; bubbles sometimes emerge from the vent for as long as ten minutes after restoration of ventricular output. When unexpected ventricular fibrillation or depressed output occurs during this period, air is often seen in a branch of the right coronary artery. The frequent occurrence of depressed myocardial performance following valve replacement is probably related to this insidious complication.

Monitoring of left atrial pressure has proved to be the only reliable guide for fluid (blood) replacement and for determining the need for inotropic drugs. We have treated borderline patients in whom adequate perfusion could be achieved only by transfusion to a left ventricular filling pressure of 25 cm of water. However, the further addition of as little as 100 ml of blood may produce a sharp rise in atrial pressure and pulmonary edema.

Adequacy of perfusion is poorly reflected by peak systolic blood pressure which is maintained by reflex vasoconstriction. Mean arterial pressure monitored from an indwelling cannula is a more significant measurement but still does not correlate well with cardiac output. We firmly believe that peripheral vasoconstrictor drugs are contraindicated in the long-term management of cardiogenic shock because they cause metabolic acidosis. A clear sensorium, adequate urinary output, warm skin and palpable peripheral pulses reflect satisfactory circulation regardless of blood pressure. Absence of these signs should cause concern even if blood pressure is normal or elevated.

REFERENCES

1. Ebert, P. A., Jude, J. R., and Gaertner, R. A.: Persistent hypokalemia following open-heart surgery, Circulation, 31:137-143 (Suppl. I), April 1965.

2. Goldfarb, D., and Bahnson, H. T.: Early and late effects on the heart of small amounts of air in the coronary circulation, J. Thoracic Cardiovasc. Surg., 46:368-378, September 1963.

3. Groves, L. K., and Effler, D. B.: A needle-vent safeguard against systemic air embolus in open-heart surgery, J. Thoracic Cardiovasc. Surg., 47:349-355, March 1964.

4. Kirklin, J. W., and Theye, R. A.: Cardiac performance after open intracardiac surgery, Circulation, 28: 1061-1070, December 1963.

5. Roe, B. B., Hutchinson, J. C., and Swenson, E. E.: High-flow body perfusion with calculated hemodilution, Ann. Thoracic Surg., 1:581-589, September 1965.

6. Roe, B. B., and McKay, L. M.: An improved watertight coronary cannula, J. Thoracic Cardiovasc. Surg., 43:139-140, January 1962.

7. Spencer, F. C., Trinkle, J. K., Eiseman, B., Reeves, J. T., and Surawicz, B.: Aortic valve replacement in elderly patients with cardiac failure, J.A.M.A., 189:103-107, 13 July 1964.

Radiographic Detection of Plastic Catheter Embolus

DAVID R. COBLENTZ, M.D., *Los Angeles*

■ *Embolization of portions of a plastic intravenous catheter is not a rare occurrence. When plain films do not serve to determine the location of the migrant tubing, special venographic and cardiopulmonary angiographic studies are helpful.*

POPULAR USE OF THE plastic polyethylene catheter for intravenous therapy has resulted in a variety of complications.[4,6,8] Reported experience is beginning to indicate that embolization of the catheter into the deep venous system is not uncommon.* Difficulties in localization of the fragment, which is nonopaque, can be reduced by the proper selection of radiographic studies, based initially on plain films. There are special radiographic procedures for use when plain films do not show where the piece of catheter is lodged.

One of the causes of catheter embolus is severance of the catheter on the sharp beveled needle used to introduce the catheter into the vein. This may happen during withdrawal of the catheter through the needle or following displacement of the plastic guard from the needle point. Another is fracture of the tubing from repeated flexion of the catheter across a joint. There are also reports of accidental cutting of the tubing during dressing changes. In some reported cases the cause of embolization could not be determined. Detection is often clinically important.

The following seven cases are presented to illustrate the roentgenographic patterns in the problem of determining where the migrating catheter fragment is.

Reports of Cases

CASE 1.—A six-year-old girl was admitted with an injury of the left extremity. An intravenous catheter that was placed in the right arm for maintenance therapy was severed during adjustment. Immediately a tourniquet was applied to

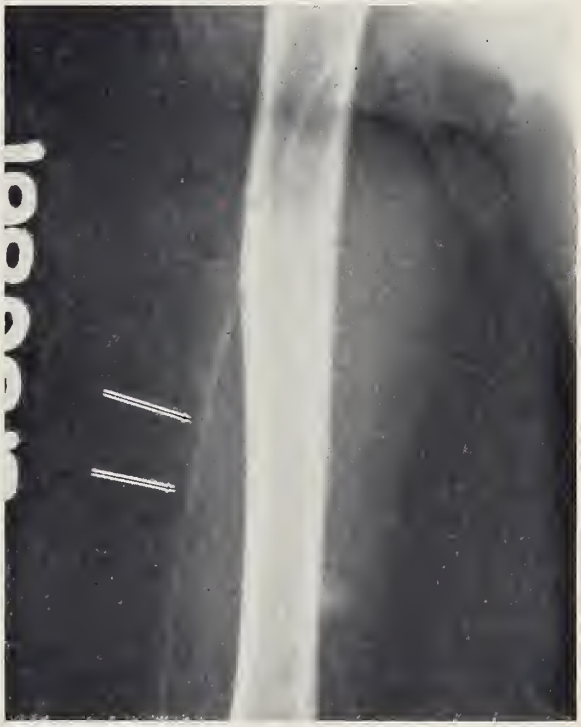


Figure 1.—(Case 1) Plain film soft-tissue study. The catheter was easily identified (arrows). A tourniquet was applied to the proximal arm to arrest central migration.

Presented before the Section on Radiology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Department of Radiology, Los Angeles County General Hospital, 1200 North State Street, Los Angeles 90033.

*Reference Nos. 1, 2, 5, 10, 11, 13.

the arm proximally. When attempts to palpate the severed fragment failed, soft-tissue x-ray examination showed it in the cephalic vein (Figure 1). The vein was opened surgically at the site and the catheter was removed without incident.

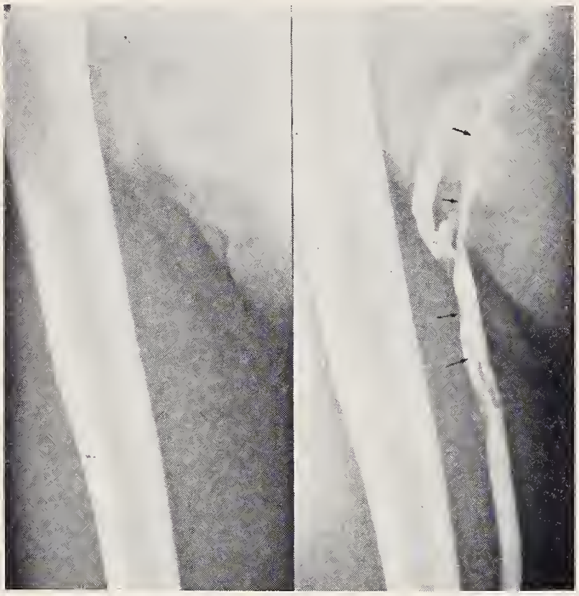


Figure 2.—(Case 3) Catheter embolus. At left, initial plain films failed to indicate site of embolus. At right, a venogram revealed catheter in the cephalic vein appearing as a linear non-branching filming defect.

Case 2.—An 80-year-old man was admitted in severe cardiac failure. On films of the chest a

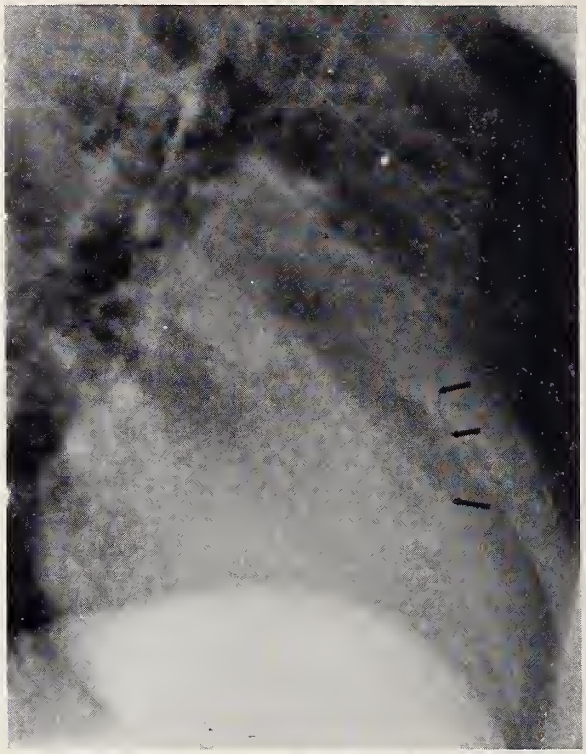


Figure 3.—(Case 4) Plain film of chest. The catheter fragment was identified within the heart on the lateral view.

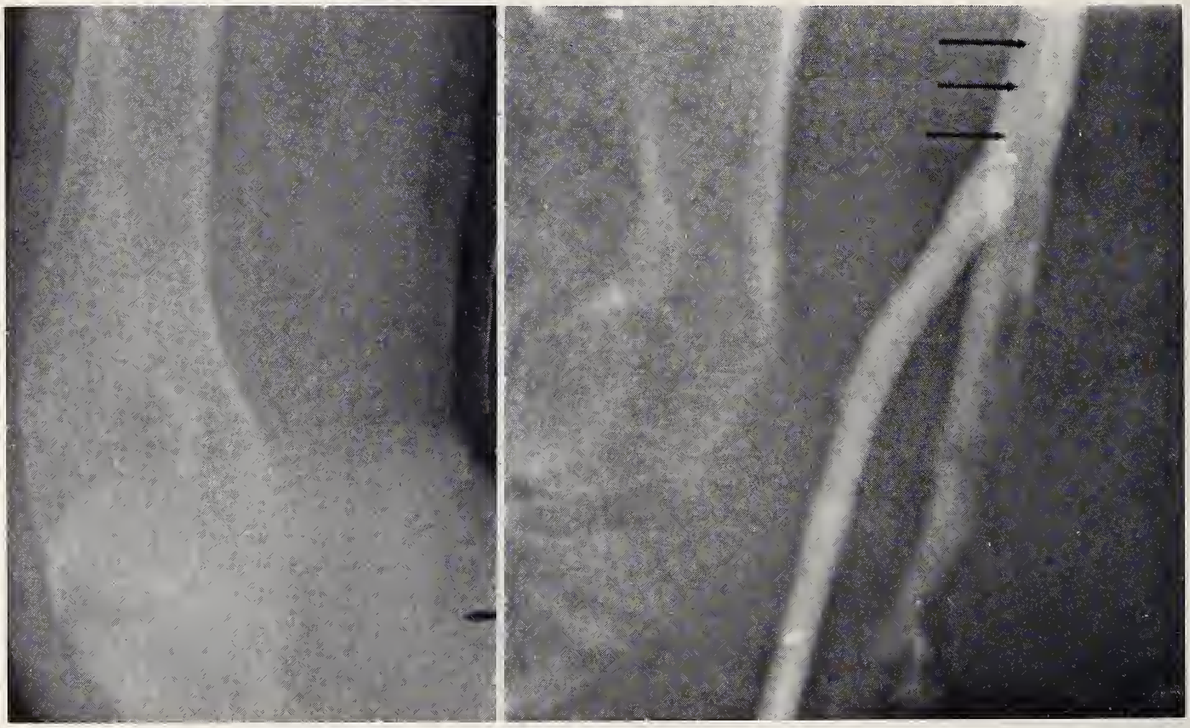


Figure 4.—(Case 5) Plain film failed to reveal location of catheter fragment. Venogram showed it within an anticubital vein.

catheter fragment was identified in a right upper lobe pulmonary artery. How the catheter embolism came about was not known. The patient died of intractable heart failure soon after the x-ray studies identified it. Necropsy confirmed the presence of the catheter fragment described.

CASE 3.—A man 70 years of age was admitted following a gunshot wound in the abdomen. During a stormy postoperative course an intravenous catheter was noted to have been displaced. Initial plain films did not conclusively reveal the fragment but it was successfully demonstrated by venography (Figure 2). The catheter fragment was removed by cut-down.

CASE 4.—A 47-year-old man was admitted in severe dehydration and electrolyte imbalance. A catheter that was placed for intravenous therapy was severed on the sharp needle bevel. A lateral film of the chest showed the fragment lodged within the heart (Figure 3). It was removed by cardiotomy without complication.

CASE 5.—One day after herniorrhaphy in a 58-year-old man it was noticed that a catheter had been displaced. Plain films did not show its whereabouts. Venograms showed it in an antecubital vein (Figure 4). The catheter subsequently migrated into the right ventricle and eventually into the right pulmonary artery as seen on a cardiopulmonary angiogram. No attempt was made to remove it. At last report, three months later, the patient was well.

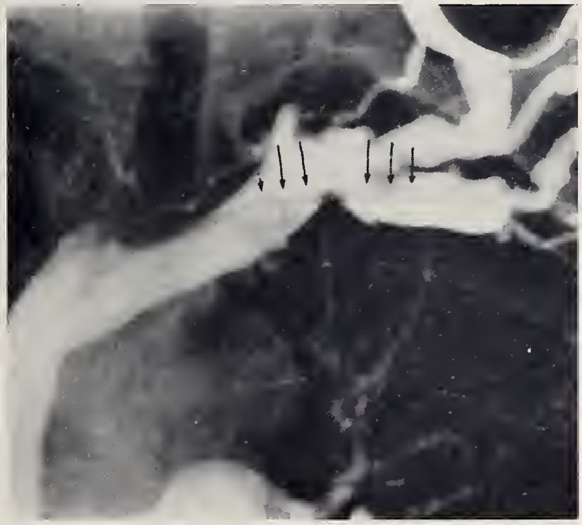


Figure 5.—(Case 6) In a venogram, a portion of 30-cm catheter fragment was seen as a linear filling defect within the left subclavian vein and superior vena cava.

CASE 6.—A 71-year-old woman was admitted to hospital with small bowel obstruction five weeks after resection of the colon. A 30-inch section of a venous cut-down catheter that had been accidentally cut off during a dressing change had migrated centrally. Plain films did not show where it was. A venogram showed it within the superior vena cava and right atrium (Figure 5). It was removed before operation to free the bowel obstruction was undertaken.

CASE 7.—A man 66 years of age was admitted to hospital in alcoholic coma and severe dehydration. An intravenous catheter that was being placed for therapy was severed by the needle. Plain films did not determine the site of the migrating portion, but a pulmonary angiogram showed it in the right pulmonary artery, without evidence of obstruction (Figure 6). The patient was asymptomatic and discharged to the clinic.

Discussion

Methods of radiographic detection of the plastic catheter are based initially on routine plain film studies of probable sites of embolization.[2] The

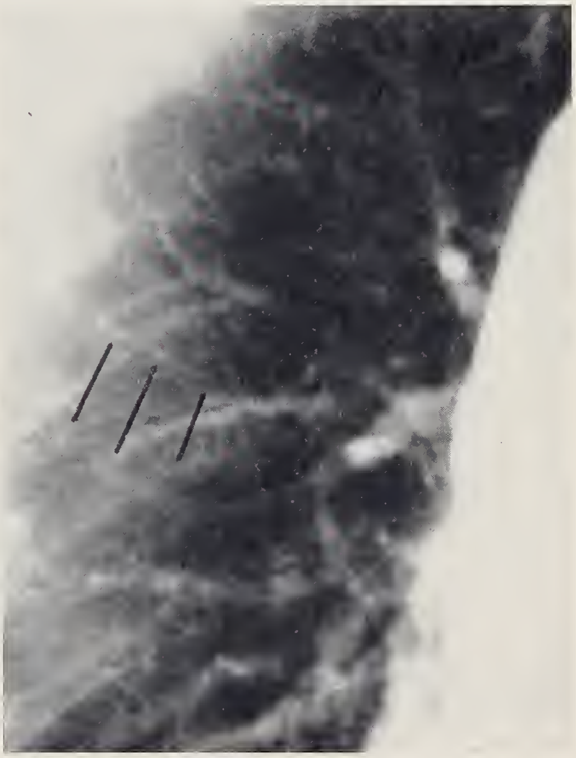


Figure 6.—(Case 7) Pulmonary angiogram, the catheter fragment was not seen on plain films. On angiographic study it appeared as a linear, non-branching filling defect within a right pulmonary artery branch.

extremities are best studied with good soft-tissue technique and good collimation to reduce scatter and enhance the difference in translucency between the tubing and fat. Contrast of the low opacity catheter is greatest in the 60 to 70 KV range, and tends to decrease with KV above 90. After careful study based on suspicion of embolization, films of the chest taken with 90 to 120 KV technique usually demonstrate the position of the tubing.

Special radiographic studies are indicated when plain films fail to demonstrate the catheter fragment.[1,2] The venogram is performed by intravenous injection of contrast material, distal to the site of suspected embolus. This is not without complication, as the catheter may be displaced centrally during or immediately after injection. Hence it is necessary to be prepared to carry out further angiographic studies should central displacement occur.

Cardiopulmonary angiography has been successful in demonstrating the catheter fragment in the superior vena cava, in the right atrium and ventricle and in pulmonary arteries. The catheter appears as a linear filling defect within the injected contrast material.

Complications of catheter embolus are most frequently a response to a septic foreign body within the venous system, right heart or vessels of lesser circulation.[9,10] Two cases of fatal perforation of the heart have been reported.[3,7] There have been no reports of acute pulmonary vascular occlusion caused directly by the plastic fragment, but since propagation of thrombus from the catheter embolus lying within the superior vena cava or right heart has been described,[1] significant vascular occlusion might occur from that source. On the other hand, long-term survival has been reported [11,12] with the fragment of tubing left in place. In these cases the clinical course may be uneventful.

Clinicians must reevaluate the practical indications for use of the plastic intravenous catheter and the method of application to limit the frequency of complication.

REFERENCES

1. Barry, Wm. F., McIntosh, H. D., and Whalen, R. E.: Catheter Embolus; A radiographic demonstration of a polyethylene catheter lying free in superior vena cava, New Engl. J. Med., 267:1194-1196, 6 December 1962.

2. Bennett, P. J.: Use of intravenous plastic catheters, Brit. Med. Jour., 2:1252-1253, 16 November 1963.

3. Brown, C. A., and Kent, A.: Perforation of right ventricle by polyethylene catheter lost during intravenous therapy, South. Med. J., 49:466-467, May 1956.

4. Dreskin, J.: Bacterial contamination of indwelling intravenous polyethylene catheters, J.A.M.A., 185:966-968, September 1963.

5. Edwards, J.: Intracath embolus—A rare complication of indwelling catheters used for intravenous therapy, South. Med. J., 56:1354-1356, December 1963.

6. Indar, R.: Dangers of indwelling polyethylene cannulae in deep veins, Lancet, 1:284-286, February 1959.

7. Johnson, C. E.: Perforation of right atrium by a polyethylene catheter, J.A.M.A., 195:176-178, 14 February 1966.

8. Scharf, F. L., and Bergman, B. J.: Some complications in use of indwelling intravenous polyethylene catheters, Med. Serv. J. Canada., 15:724-730, January 1959.

9. Steiner, M. L., Bartley, T. D., Byers, F. M., and Krovitz, L. J.: Polyethylene catheter in the heart, J.A.M.A., 193:1054-1056, 20 September 1965.

10. Taylor, F., and Rutherford, C. E.: Accidental loss of plastic tube into venous system, Arch. Surg., 86:177-179, January 1963.

11. Trusler, G. A., and Mustard, W. T.: Intravenous polyethylene catheter successfully removed from the heart, J.A.M.A., 193:1054-1056, 20 September 1965.

12. Tulgan, H.: Prolonged survival after catheter embolus, Ann. Int. Med., 59:564-565, September 1964.

13. Turner, D. D., and Sommers, S. C.: Accidental passage of a polyethylene catheter from cubital vein to right atrium, New Engl. J. Med., 251:744-745, 28 October 1954.

Experimental Pulmonary Air Embolism in Dogs

CHARLES C. WYCOFF, M.D., AND JOHN E. CANN, M.D., *San Francisco*

■ *Air infused into the jugular vein of dogs at a constant rate for one hour produced transient hypotension, modest elevation of the systemic venous pressure and a considerable fall of the arterial oxygen tension. All of these measurements returned almost to normal on the termination of the infusion. A lethal rate of infusion, 0.69 ml of air per kg of body weight per minute, produced heart failure with a decided rise of systemic venous pressure and fall of blood pressure. The pre-failure oxygen pressure did not fall to a lethal level. Six and a half minutes was the longest time that the characteristic murmur could be heard after the cessation of infusion of non-fatal doses of air.*

AIR EMBOLISM has been reported in many clinical situations, and among the causes are abortion,[25] douching,[7] gunshot wound of the neck,[4] operation on the bladder,[9] root canal therapy,[23] craniotomy with pressurized drill,[6] neurosurgical procedures,[12,16] operations on the head and neck, antrum lavage, air insufflation of the bladder and joints, pneumoperitoneum, vaginal insufflation with powder blowers, and blood donations.[5] Death does not always result from air embolism, particularly when it is diagnosed immediately and vigorously treated.[5,6,15,16,26]

Many studies have been done with animals to determine the cause of death in air embolism of the right heart. Richardson[22] injected air into the veins of dogs and summarized his work conclusively: "The pulmonary capillary bed acts as an effective barrier to intravenous air. Death occurs from failure of the pulmonary circulation." Jacques[13] observed: "The cause of death in massive pulmonary embolism presents no problem. It results from pure mechanical blockage of the lesser circulation. This results in an elevation of pulmonary artery pressure, a fall in systemic pressure, right heart dilatation and cardiac failure."

The present study was done with dogs to determine if a low arterial oxygen tension was the cause of heart failure in right heart air embolism. Progressively larger doses of air were introduced into the jugular veins of dogs until the lethal rate of infusion was reached.

Method

Each dog was anesthetized with thiopental, intubated and hyperventilated with oxygen-enriched air mixture at a terminal inspiration pressure of 20 mm of mercury. An esophageal stethoscope was placed to monitor the heart sounds. The right femoral artery was punctured with a 16-gauge

---

Presented before the Section on General Surgery at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 900 Hyde Street, San Francisco 94109 (Dr. Wycoff).

plastic needle for determining arterial pressures with a mercury manometer. The pressures were expressed as the mean of each reading. The left external jugular vein was ligated and catheterized with a 6 mm plastic tube advanced as far as the superior vena cava for determining the systemic venous pressure with a water manometer. The readings were expressed as averages in millimeters of water. The position of the tip of the catheter was checked at postmortem examination for the exact zero of the venous pressure. The right external jugular vein was punctured with a 16-gauge plastic needle for the infusion of air. The vessel was left intact to allow a normal flow of blood. The left carotid artery was ligated and catheterized with a 3 mm catheter which was introduced to the arch of the aorta for collection of blood to determine oxygen tensions.

Each dog was suspended by the muzzle so that the upper half of the body was upright. Air was infused for one hour into the right jugular vein at a constant rate by drip displacement of air from 30 ml syringes. The rate of infusion was increased in successive animals from 0.13 ml of air per kg of body weight per minute to 0.69 ml per minute. The doses in eight animals were 0.13, 0.24, 0.31, 0.36, 0.37, 0.51, 0.61 and 0.69 ml per kg per minute. Arterial blood samples for oxygen determination were taken 15 minutes before infusion began, immediately before infusion and every 15 minutes thereafter including a final sample 15 minutes after the infusion was stopped. Eight young normal animals were included in this series.

In a second series of dogs a microphone was sutured under the skin over the precordial area, and tape recordings were made during the constant infusion of air into the jugular vein.

Results

The seven dogs receiving air at the rate of 0.13 to 0.61 ml per kg per minute did not die during the experimental period. The variations of the arterial oxygen tension, systemic venous pressure and systemic arterial pressure of these animals are shown graphically (Charts 1, 2 and 3).

The systemic arterial oxygen tension fell in every instance during the infusion but rose after the infusion was stopped. The lowest level of oxygen tension was 47 mm of mercury. The tension did not rise to the pre-infusion normal in any animal during the 15-minute recovery period. The 15-minute post infusion oxygen tension varied from 74 to 119 mm of mercury. The average was 100 mm.

In all animals, the systemic arterial pressure fell immediately after the infusion was started. The

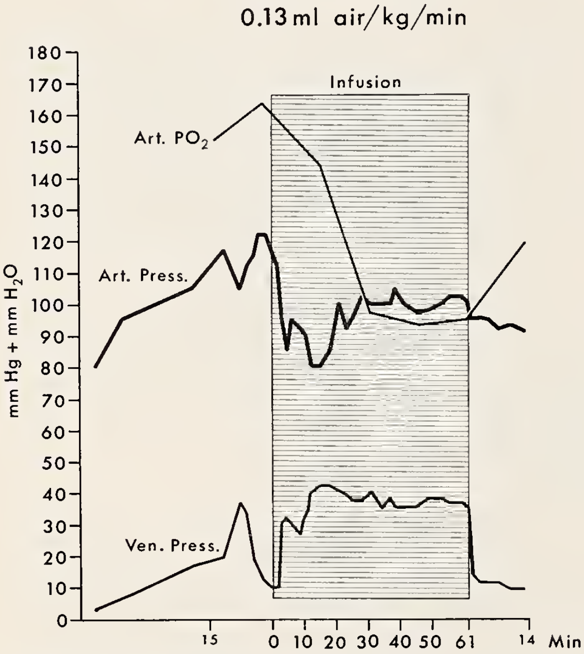


Chart 1.—The lowest rate of infusion, 0.13 ml of air per kg of body weight per minute.

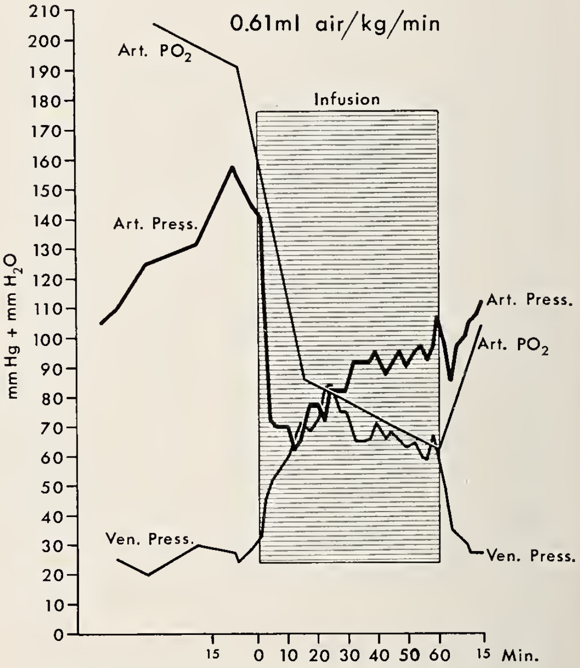


Chart 2.—The highest non-lethal rate of infusion, 0.61 ml of air per kg of body weight per minute.

lowest level to which the arterial pressure fell was 32 mm of mercury. When 30 minutes of infusion had elapsed, the blood pressure had begun to rise in all animals and had reached a near normal level by the end of the infusion. The systemic venous pressure rose rapidly after the start of the infusion. The highest level was 84 mm of water. Within 30 minutes after the start of infusion, the venous pressure in all seven animals had begun to fall but remained somewhat elevated until the cessation of infusion. After the air infusion stopped the venous pressure quickly fell to the pre-infusion normal.

The recordings of the animal that received air at a rate of 0.69 ml per kg per minute and died are shown graphically in Chart 4. The systemic arterial pressure fell initially to 25 mm of mercury, which was a lower level than was recorded for the other animals. Then the arterial pressure rose to 50 mm of mercury before it fell to a terminal level. The venous pressure rose steadily to 262 mm of water within 18 minutes and fell to 152 mm at the time the arterial pressure had fallen to a terminal level. The systemic arterial oxygen tension fell to 47 mm of mercury as the arterial pressure and venous pressure went to terminal levels. The animal died within 20 minutes from the start of the air infusion.

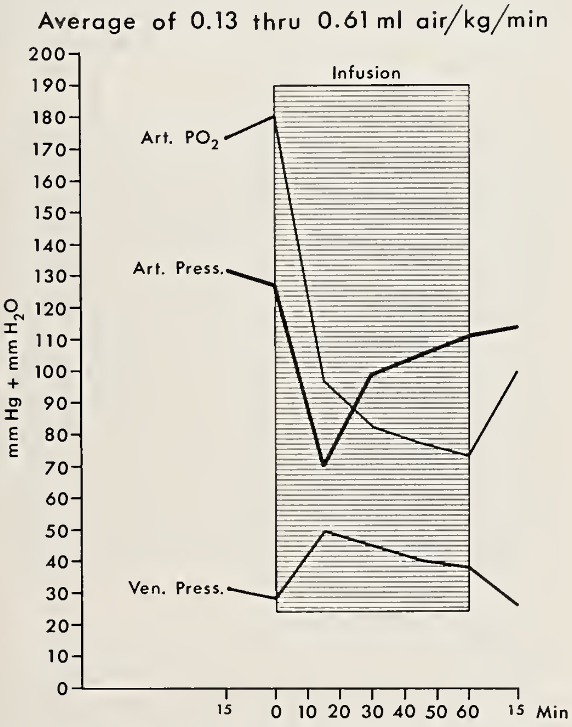


Chart 3.—The average of all non-lethal rates of infusion, 0.13 through 0.61 ml of air per kg of body weight per minute.

In the series of dogs where recordings of the heart sounds were made, the lowest rate of infusion which altered the normal heart sounds was 0.2 ml per kg per minute. The sound was a "tinkle" similar to that of water being poured into a half empty jug. As the volume of air increased, the sound of air in the heart became a "squish," and finally when the larger volumes were injected the sound became "chuck" with each heart beat. The sound became discernible in 17 minutes with the 0.36 ml per kg per minute rate of injection, in nine minutes with the 0.5 ml rate and in two minutes with the 0.61 ml rate. When the infusion of air was stopped, the air murmur began to disappear and became fainter and fainter until it could no longer be heard. Six and a half minutes was the longest that an air murmur persisted after the cessation of infusion of a non-lethal dose of air.

Discussion

Systemic Arterial Oxygen Tension

As all the animals had artificial respiration, there was no indication of respiratory changes. Studies with other dogs[27] have shown that an end respiratory pressure of 20 mm of mercury and minute rate of 14 to 16 produced a systemic arterial partial pressure of carbon dioxide of near 25 mm of mercury. In this study, lethal or near-lethal rates of infusion occasionally caused the animals to attempt to breathe despite the hyperventilation. This suggests that the level of carbon dioxide had built up to or above normal.

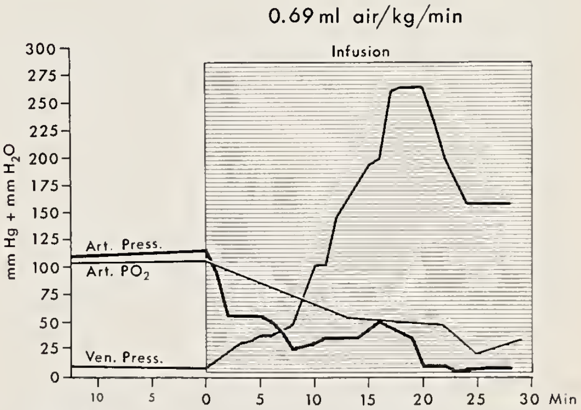


Chart 4.—The rate of infusion in dog with heart failure, 0.69 ml of air per kg of body weight per minute.

Mandelbaum[14] showed that an immediate rise of pulmonary arterial pressure follows embolization of the lung. However, he also showed that the embolic gas is not excreted in the lung but passes through to form bubbles in the pulmonary veins. The rise of pulmonary artery pressure may be due to mechanical blockage in the capillaries, but Hampton[11] showed that the rise of pulmonary artery pressure after embolization can be prevented by sectioning the vagi. Perhaps the normal pulmonary arterial pressure which is maintained by sectioning the vagi is the result of an opening of arteriovenous channels. Niden[19] demonstrated such shunts by injecting glass beads into the pulmonary circulation of dogs. He stated: "The perfused lung shows arteriovenous communications that are at least 420 micra in diameter." Richardson[22] found that in air embolism "there was a concentration of red cells in the capillaries and an absence of cells in the veins," phenomena which he attributed to pulmonary edema, although they could be due to constriction of the pulmonary capillaries.

The fall of systemic arterial oxygen tension observed in this study can be explained by the presence of pulmonary edema and by the opening of arteriovenous shunts. Even before the sound of air could be heard in the heart, crepitant rales were audible through the esophageal stethoscope. During preliminary studies, it was found that animals receiving lethal or near-lethal doses of air developed so much pulmonary edema that thin fluid bubbled out of the endotracheal tube. Other investigators have shown that air embolism produced pulmonary edema[14,22] and proliferation of the arterial intima.[1]

The return of the arterial oxygen toward normal after the cessation of air infusion can be explained as due to a reversal of the processes that produced the lowering of the oxygen tension. There probably remained a residual edema and that is why the oxygen tension did not return completely to normal.

In humans[17,20,21] as well as in animals[8,10] life has been maintained for many hours with an arterial oxygen tension of 25 mm of mercury. The arterial oxygen level of the dogs in the present study fell no lower than 47 mm of mercury; it was down to 22 mm of mercury only at death in the dog that had heart failure. In right heart air embolism produced in this study there was a continued partial oxygenation of the blood that passed through the lungs. The level of arterial oxygen was sufficient to maintain life. Therefore a reason other than low arterial oxygen tension must be found to explain the heart failure.

Durant[2] injected air into thoracotomized dogs and found an area of ischemia "just to the right of the lower reaches of the anterior descending branch of the left coronary artery" when right ventricular dilatation occurred. Durant also presented electrocardiograms showing ischemic changes of the T wave and the ST segment. Electrocardiograms of dogs in our preliminary studies also had deep inversions of the T waves, which returned to normal after the cessation of air infusion. Therefore we can assume that cardiac dilatation produces right heart ischemia. Another factor contributing to the ischemia of the right ventricle was failure of the heart to increase the cardiac output and coronary perfusion by increasing the heart rate. In fact, in every animal bradycardia developed shortly after the infusion of air began. The rates almost halved in each instance during the infusion and increased after the infusion was stopped. In the animals that died from large doses of air, the pulse gradually slowed until effective beats ceased. In none of the animals did ventricular fibrillation develop until the heart was manipulated during the resuscitation efforts, and ventricular fibrillation then was not uniformly produced.

Systemic Arterial Pressure

Preliminary studies of air embolism showed that the fall in systemic arterial pressure reversed itself within 30 minutes so an arbitrary experimental period of one hour was chosen. The return of blood pressure toward normal during the end of the hour of infusion can be explained as due to the reflex opening of arteriovenous shunts[11] and greater return of blood to the left side of the heart. However, there is also the probability that systemic vascular reflexes caused a drop of pressure early and then raised the pressure later. In addition, the return of the arterial pressure during the last half of the infusion may have been due to a reflex release of catacholamines by hypoxia.

Systemic Venous Pressure

The rise in venous pressure and sustained moderate elevation during the infusion was consistent with the idea of mechanical obstruction in the lung. It is surprising that the level of venous pressure did not rise higher in the near-lethal doses of air. The drop of venous pressure to the preinjection level further substantiates the claim that air rapidly leaves the heart even in the upright position at these rates of infusion.

Failure of Normal

The systemic venous pressure rose above a normal level in the animal receiving 0.69 ml of air per kg of body weight per minute. The abnormal elevation occurred after the systemic arterial pressure had fallen below 40 mm of mercury and even though the arterial pressure rose to 50 mm, the venous pressure continued to rise. Two abnormal animals were infused with air and their courses were quite similar to that of the normal animal that had heart failure. The abnormal animals were old dogs, as evidenced by the front lower incisors being worn down almost to the gum. They were infused with 0.4 and 0.44 ml of air per kg per minute. The systemic arterial blood pressure in both fell to below 40 mm of mercury within 18 minutes after the start of infusion, at which time the systemic venous pressures were 70 and 120 mm of water but the venous pressures continued to rise to 282 and 245 mm of water. Shortly after these elevated levels were reached, the arterial pressures fell to zero and the venous pressures fell to 150 and 130 mm of water. At no time did the arterial oxygen pressure fall below 64 mm of mercury in the old dogs.

Additional Observations

All the studies in this series were acute experiments. Therefore there was no opportunity to observe the late effects of capillary obstruction described by Mendelbaum[14] and Richardson.[22] These late complications were pulmonary congestion, atelectasis, pulmonary edema and bronchopneumonia.

Occasionally air could be heard as a bubbling sound when it passed down the jugular vein. The bubbling occurred only during the expiratory phase of the respirator. The valve used was a non-rebreathing valve which allowed the positive pressure of the respirator to inflate the lungs; but expiration was directed to the atmospheric pressure. There was no creation of a negative intrathoracic pressure by the respirator. As the infusion of air was by water displacement of air, a positive infusion pressure forced the air to overcome any rise of venous pressure. When a small column of water was placed in the plastic infusion tubing, it moved along with the infused air and only moved during the expiratory phase of the respirator. The positive phase of the respirator prevented any infusion of air during respiratory inflation.

Richardson observed that the level of the systemic arterial blood pressure before infusion determined the resistance of the dog to the infusion of air. We had the same impression and noted that the dog receiving 0.61 ml of air per kg per minute had an initial blood pressure of 142 mm of mercury and the air murmur cleared in two minutes, whereas the dog receiving 0.51 ml per kg per minute had an initial arterial pressure of 92 mm of mercury and the air murmur did not clear until six and a half minutes had elapsed.

In other experiments, we found that 0.3 ml of air per kg per minute caused the death of a dog whose chest had been opened. Durant quickly injected large volumes of air and found that smaller volumes produced fatalities in dogs with open chests but larger volumes did not produce fatalities in dogs with closed chests.[2] The stress and failure of the heart following air embolism of the right heart are influenced by many factors. Richardson,[22] Mandelbaum[14] and Boerema[1] showed that the volume of air and the speed of injection are important factors in the production of heart failure. The larger the volume of air and the more rapidly it is injected, the more likely failure. Also the partially collapsed lungs following thoracotomy increase the likelihood of fatality from air embolism.

There are no reports in the literature of incompetent valves increasing the risk in air embolism but it seems reasonable to assume that such would be the case. Any factors which increase the movement of air through the heart and lungs are likely to reduce the possibility of fatality. These factors are: Adequate blood volume, normal myocardial contractile force, normal or elevated blood pressure, competent valves, low pulmonary vascular resistance, mild vagal reflex and patent pulmonary arteriovenous shunts. The factors favoring heart failure from a given amount of air embolism are: Diminished circulating blood volume, hypotension, poor myocardial reserve, incompetent valves, high pulmonary vascular resistance, active vagal reflex and small pulmonary arteriovenous shunts.

Another factor that can contribute to fatality with a small volume of air entering the right heart is a patent foramen ovale. Such a patent opening would allow air to go directly from the right atrium into the left atrium and thereby produce systemic arterial embolism. Smaller volumes of air in the coronary and cerebral arteries are required to produce fatality than the amounts necessary to cause death in the pulmonary circulation.[3,24] On the basis of studies in cats, Moore calculated that over 37.5 ml of air passing through the left side of the heart would be required to produce fatality in a 150-pound man.[18]

A review of some of the physiologic features associated with air embolism of the right heart will clarify the steps taken in treating the clinical situation. When air ceases to go into the heart, the murmur stops in a very short time, provided the blood pressure is not at a shock level and the heart has not dilated to a point of failure with a high venous pressure. The cessation of the murmur is assumed to be due to the passage of air from the heart into and through the pulmonary circulation. The movement of air through the heart occurs only if the heart does not fail. Pronounced venous distension is a manifestation of heart failure. Hypotension is also a sign of the heart failure.

Turning the patient onto the left side increases the amount of air that can be tolerated in the right heart. Experimental data have demonstrated that, on turning, the large bubble of air in the pulmonary conus rises into the right ventricle, allowing blood to flow through the heart.[2] Clinical experience has shown that the patient turned to the horizontal position with the left side down responds quickly from the hypotension of air embolism.[5,16]

Very large volumes of air, slowly or rapidly introduced, produce acute right heart failure. This situation has been effectively treated by opening the heart to allow the air to escape from the atrium[15] and by needling the heart to remove the air.[26]

Diagnosis of air embolism is best made by listening for the sound of the characteristic murmur. This can be done by having an esophageal stethoscope in place when patients are operated on in the sitting or semisitting position. Also, when hypotension develops in situations in which air embolism can occur, the precordium should be auscultated. When the characteristic murmur is heard, the following steps should be taken in sequence to establish a normal blood pressure:

1. Stop air entry into the vein.
2. Turn the patient into the horizontal position with the left side down.
3. Aspirate the air from the heart.
4. Perform external cardiac massage.

Acknowledgment: This study was financed with funds made available by the School of Dentistry, College of Physicians and Surgeons, University of the Pacific.

REFERENCES

1. Boerema, B.: Appearance and regression of pulmonary arterial lesions after repeated intravenous injection of gas, J. Path. Bact., 89:741, 1965.

2. Durant, T. M., Long, J., and Oppenheimer, M. J.: Pulmonary (venous) air embolism, Amer. Heart J., 33: 269, March 1947.

3. Durant, T. M., Oppenheimer, M. J., Webster, M. R., Long, J.: Arterial air embolism, Amer. Heart J., 38:481, 1949.

4. Ellis, G. R., and Brown, J. R.: Massive air embolism due to gunshot wound. J.A.M.A., 189:953, 21 September 1964.

5. Emery, E. R. J.: Air embolism. A report of two cases, one treated successfully, Anaesthesia, 17:455, 1962.

6. Ericsson, J. A., Gottlieb, J. D., and Sweet, R. B.: Closed chest cardiac massage in the treatment of venous air embolism, New Engl. J. Med., 270:1353, 1964.

7. Glassy, F. J. :Coroner's Corner, Med. Times, 91: 63a, December 1963.

8. Glick, G., Plauth, W. H., and Braunwald, E.: Circulatory response to hypoxia in unanesthetized dogs with and without cardiac denervation, Amer. Physiol., 207: 753, October 1964.

9. Goddard, D. W., and Moffett, J. D.: Fatal air embolism during urologic operation, J. Urol., 73:613, March 1955.

10. Gorlin, R., and Lewis, B. M.: Circulatory adjustments to hypoxia in dogs, J. Appl. Physiol., 7:180, September 1954.

11. Hampton, J. W., Jacques, W. E., and Bird, R. M.: Influence of vagotomy on experimentally induced pulmonary hypertension, Physiologist, 3: 3, 73, August 1960.

12. Hunter, A. R.: Air embolism in the sitting position, Anaesthesia, 17:467, October 1962.

13. Jacques, W. E.: Recent advances in thrombo-embolism, J. Okla, Med. Assn., 56:522, 1963.

14. Mandelbaum, I., and King, H.: Pulmonary air embolism, Surg. Forum, 14:236, 1963.

15. Marchand, P., Van Hasselt, H., and Luntz, C. H.: Massive venous air embolism, S. Afr. Med. J., 38:202, 28 March 1964.

16. Marshall, B. M.: Air embolism in neurosurgical anesthesia, its diagnosis and treatment, Canad. Anaesth. Soc. J., 12:255, May 1965.

17. McNicol, M. W., and Campbell, E. J. M.: Severity of respiratory failuure. Arterial blood-gases in untreated patients, Lancet, 1:336, 13 February 1965.

18. Moore, R. M., and Braselton, C. W.: Injections of air and of carbon dioxide into pulmonary vein, Ann. Surg., 112:212, August 1940.

19. Niden, A. H., and Aviado, D. M.: Effects of pulmonary embolism on the pulmonary circulation with special reference to arteriovenous shunts in the dog, Circ. Res., 4:67, 1956.

20. Refsum, H. E.: Acid-base status in patients with chronic hypercapnea and hypoxaemia, Clin. Sci., 27:407, 1964.

21. Refsum, H. E.: Relationship between state of consciousness and arterial hypoxaemia and hypercapnea in patients with pulmonary insufficiency, breathing air, Clin. Sci., 25:361, December 1963.

22. Richardson, H. F., Coles, B. C., and Hall, G. E.: Experimental gas embolism: I. Intravenous air embolism, Canad. Med. Assn. J., 36:584, June 1937.

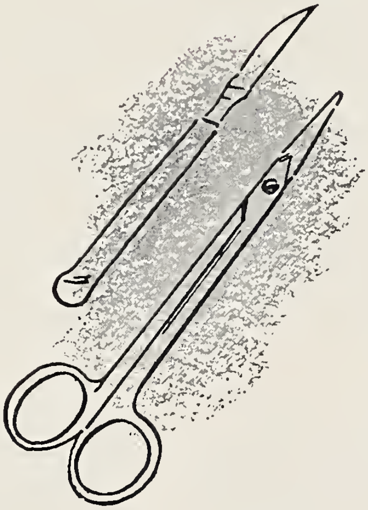
23. Rickles, N. H., and Joshi, B. A.: Death from air embolism during root canal therapy, J. Amer. Dent. Assn., 67:397, September 1963.

24. Rukstinat, G.: Experimental air embolism of the coronary arteries, J.A.M.A., 96:26, 3 January 1931.

25. Shapiro, H. A.: The diagnosis of death from delayed air embolism, J. Forensic Med., 12:3, March 1965.

26. Stallworth, J. M., Martin, J. B., and Postlethwait, R. W.: Aspiration of the heart in air embolism, J.A.M.A., 143:1250, 1950.

27. Wycoff, C. C.: Hypothermia: Ventricular fibrillation during hyperventilation, N.Y. State J. Med., 62:217, 15 January 1962.



Treatment of Circulatory Disorders of The Lower Extremities

HAROLD M. SCHNEIDMAN, M.D., *San Francisco*

■ *Successful treatment of the cutaneous changes in patients with arterial insufficiency and venous insufficiency is enhanced by a knowledge of (1) the physiology of the blood vessels in health and in disease (2) the pathologic changes underlying these disorders and (3) the side reactions of drugs as well as their efficacy.*

Treatment of stasis dermatitis often requires elevation of the involved leg at hourly intervals during the days, especially in patients who must continue to work and who must stand for long periods.

In patients with stasis dermatitis, above-the-knee elastic stockings can produce a tourniquet effect in the popliteal space and can be hazardous.

When the cutaneous changes do not heal properly, the physician must be alert to factors which, although seemingly minor, may mean the difference between a successful short course of treatment and chronicity.

SINCE CARE OF patients with cutaneous manifestations of arterial insufficiency, thromboangiitis obliterans, livido reticularis and venous disease is in the province of dermatology, dermatologists need special knowledge of physiological principles pertaining to these conditions, and of the actions and side reactions of certain drugs.

The sites of pathologic changes in these diseases are as follows:

	Arteries	*Veins*	*Capillaries*
Arteriosclerosis obliterans (AO)....	+		
Thromboangiitis obliterans (TAO)	+	+	
Livido reticularis	+		+
Stasis dermatitis................................		+	

AO and TAO are characterized by obstruction and complete occlusion of the lumen of the vessel supplying or returning blood to or from a limb. Insufficient flow of blood results in insufficient delivery of oxygen to tissue. With the limb at rest, this may cause no symptoms, but on walking or other exercise, intermittent claudication may occur. If flow of blood is severely limited, tissue necrosis and ulceration may appear. Diabetes may hasten the disease process.

Medical treatment for AO and TAO is of three categories: Preventive and protective measures, drug therapy and physical therapy.

As a part of prevention it is necessary to determine whether diabetes or high cholesterolemia is a factor. Diabetic neuritis may account for the symptoms, and corrective measures, including vitamin B_1 injections, may be beneficial. While the relationship between cholesterol and atherosclerosis remains a controversial subject, if cholesterol is found to be elevated on two determinations, a rigid low cholesterol diet is needed. If the patient is obese, the diet must be governed. A high protein diet is beneficial because the high specific dynamic action of protein has been shown to increase the circulation to the extremities. It is important for the physician to be practical in dietary measures.

Walking is permissible as tolerated. It should not be proscribed, particularly for elderly patients, for once they are confined to bed they tend to stay there. The patient may walk long distances provided the pace is slow and he stops when pain appears. This will allow collateral circulation to develop to meet the needs of the limb.

Local pressure must be avoided. Patients must be warned against too firm or too soft a mattress, tight shoes, massage and even crossing of the legs. Application of heating pads and hot water bottles to the skin of the legs impedes tissue healing. Applying heat to the back or abdomen increases peripheral circulation through reflex vasodilation.

Presented before the Section on Dermatology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 490 Post Street, San Francisco 94102.

The use of tobacco is harmful. The prolonged vasoconstriction which results from smoking may produce a thrombus or initiate gangrene. TAO will not heal unless tobacco is stopped completely.

The foregoing are the main preventive and protective measures, although there are others.

Drug Therapy of AO and TAO

Drugs used in the treatment of AO and TAO includes the following groups: Vasodilators, anticoagulants, antibiotics, hormones, steroids, vitamins, local agents.

The vasodilators act centrally, at sympathetic ganglia and directly on vessels.

Alcohol is the best example of a centrally acting vasodilator. Heating the body at the same time of alcohol intake enhances the degree of vasodilatation. One ounce four times daily is the usual prescription. Examples of agents which block the sympathetic ganglia are tolazoline (Priscoline®), phenoxybenzamine (Dibenzyline®), azapeptine phosphate (Ilidar®) and phentolamine (Regitine).

These drugs block the sympathetic nerve activity without having that effect on para-sympathetic nerves. Priscoline® is a more effective dilator of the lower than of the upper extremities. The usual prescription is 25 mg or 50 mg three times daily. Dibenzyline® is usually prescribed in doses of 10 mg three times daily and Ilidar® is given in a dose of 75 mg three times a day.

The sympathetic blocking agents are of unquestioned benefit in functional vasospastic disease. In organic arterial diseases such as AO and TAO, the benefit probably derives from their action on the functional vasospastic component of these diseases.

Examples of vasodilators acting directly on the vessel wall are nicotinyl alcohol (Roniacol®) and nitroglycerin. Roniacol usually is prescribed in dosage of 100 mg three times daily. The drug has side effects such as generalized flushing and tingling, which often disappear if the drug is continued. Nitroglycerin is more often used for its effect on the cardiac vessel wall than for its peripheral effect.

Anticoagulants have a definite place in the treatment of acute vascular disorders and in chronic peripheral disorders when thromboembolic phenomenon are common. Close supervision is necessary with these agents and they should be prescribed only by one experienced in their use and thoroughly familiar with the side reactions.

Antibiotics are indicated in the presence of ulcers and exudative dermatosis. Fungous infections are more likely to occur in the digital interspaces of patients with AO and TAO than in normal persons. Local therapy is often efficacious in control of mycosis, but it may be more practical and simple to prescribe intermittent courses of griseofulvin.

There is no specific benefit from multiple vitamin therapy. However, vitamin B_1 is helpful in diabetic neuritis and it may benefit patients with vague symptoms of neuritis.

Steroids are of no value in AO and TAO when given orally but are helpful in topical preparations.

As to local therapy, the usual principles and techniques in the care of acute and chronic dermatitis and ulcers apply. Too vigorous massage of the limb and compression for extended periods are deleterious. The protolytic and debridement agents are occasionally helpful in the treatment of ulcers.

Physical Measures

Physical measures include heating the body, postural exercises and use of an oscillating bed. Postural exercises involve maintaining the legs in a horizontal position for ten minutes; then the legs are held down for ten minutes. Alternating these positions for one hour in the morning and one hour in the afternoon is often helpful in relieving pain and congestion. Applying a heating pad at moderate temperature to the sacrum or the abdomen for 15 minutes four times a day may be helpful. Although its main value is psychological, the Sanders oscillating bed is worthy of mention. It teeters slowly, head to foot, for timed periods, keeping the patient's feet up long enough to accomplish venous dumping but not so long as to provoke ischemia, then down long enough to accomplish gravitational pull of blood into the limb but reversing before venous edema might begin.

Livido Reticularis

Livido reticularis in contrast to AO and TAO is predominately a vaso-spastic disease involving young people and mainly women. It persists for many years and is usually benign. However, in a small proportion of cases painful ulceration may appear.

The disease is due to a spasm or, less often, to organic occlusion of the arterioles with concomitant dilatation of the capillaries and venules. A mottled blueness of the legs and arms appears.

The peripheral pulses become faint and the feet and hands become cold, moist and pale. A slight breeze or slight chilling is sufficient to provoke this reaction.

The disease is classified into three categories:

1. *Cutis marmorata* in which the symptoms disappear on warming the limb.
2. *Livido reticularis ideopathica,* the symptoms of which persist in spite of warming the limb.
3. *Livido reticularis symptomatica*, in which the cutaneous symptoms occur in association with a serious underlying disease such as lupus erythematosus or periarteritis nodosa.

Therapy is directed at avoidance of chills and keeping warm. Vasodilating drugs are helpful in small doses. A complete medical evaluation is essential to rule out associated disease.

Recent preliminary studies show that the rauwolfia compounds cause livido reticularis to disappear.

Stasis Dermatitis and Stasis Ulcers

Seventeen per cent of the population has varicose veins. This represents a formidable source of disability. Some persons are born with weak venous valves. In some, the valves are absent in certain segments, and in some the venous walls are weak and after years of dependency they sag. These are the key etiological factors in the stasis syndrome. As a result of these diseased valves, the flow of blood is reversed, the pressure in the veins is increased, drainage of fluid is interfered with, waste products accumulate and stasis dermatitis ensues. If the condition is intense, necrosis of tissue occurs, and then ulceration.

Numerous therapeutic programs are currently in use but none can succeed unless edema is first controlled.

Above-the-knee stockings can be a hazard because of tourniquet effect in the popliteal space, especially when the knee is bent. Knee-length stockings are sufficient.

In patients with arterial insufficiency, elastic stockings or bandages are poorly tolerated and may initiate a clot.

If the patient complains of pain and discomfort from wearing elastic supports, deep venous occlusion is likely.

The dermatitis from stasis improves with rest and elevation of the limb. In cases of severe dermatitis seven to ten days in bed is more valuable than seven to ten months of ambulatory office care.

Treatment of Stasis Ulcers

In dealing with small stasis ulcers, I cleanse twice daily with hydrogen peroxide and then apply sterile Gelfoam powder mixed with Neosporin® powder.* This is followed by an elastic bandage or elastic stocking.

Pinch grafts applied to the ulcer as an office procedure are remarkably effective.

Large stasis ulcers will often require grafting and stripping of veins but a vigorous attempt to heal the ulcer by other means is justified.

The modalities which I use most often are as follows:

1. *Gelfoam powder and Neosporin powder:* Very effective in small ulcers, often effective in larger ulcers.
2. *Unna Boot:* This zinc-gelatin bandage must be applied after the leg has been elevated for at least 15 minutes. The ulcer may be covered directly with the boot.
3. *Gold leaf:* A thin layer of 23 karat gold film is applied to the ulcer. Before application the ulcer is dabbed with 70 per cent alcohol, and after application pressure is applied with a cotton ball. The gold leaf is held in place with roller gauze. This procedure is repeated every five to seven days. In my experience it has been remarkably effective.
4. *Adhesive tape method:* The ulcer is covered with adhesive tape which is left in place for five to seven days.

If after six weeks the ulcer shows no sign of healing, skin grafting must be considered.

As to venous operations, if the symptoms are minor to moderate, operation can be deferred. While the symptoms may lessen, the etiological mechanisms will never disappear and operation early might prevent future dermatitis and trouble. My preference is for venous ligation and venous stripping since this gives more complete eradication of the diseased organs and diminishes the need for future sclerosing injections.

GENERIC AND TRADE NAMES OF DRUGS

Tolazoline—*Priscoline.*
Phenoxybenzamine—*Dibenzyline.*
Azapeptine phosphate—*Ilidar.*
Phentolamine—*Regitine.*
Nicotinyl alcohol—*Roniacol.*
Polymyxin B sulfate, neomycin sulfate and zinc bacitracin—*Neosporin powder.*

---

*A mixture of polymyxin B sulfate, neomycin sulfate and zinc bacitracin.

Recent Advances in the Treatment of Hypertension

WILLIAM M. SMITH, M.D., *San Francisco*

■ *The most exciting recent advances in the treatment of hypertension have been in our appreciation of the probable involvement of the kidney in all forms of hypertensive disease, in our improved understanding of the basic underlying mechanisms in some forms of the disease, and in the clarification of mechanisms of action of some of the most useful drugs.*

This permits us to diagnose more accurately and to administer therapy more rationally.

Treatment of the mild and moderate stages of the disease, although not yet proved to reduce mortality and morbidity, would appear to be justified since pressure control is readily achieved with the relatively non-toxic drugs currently available.

A RELATIVE MORATORIUM on the appearance of new agents since the recent enactment of New Drug Legislation affords opportunity to reflect on "recent advances" as they pertain to new concepts and new understanding rather than new drugs. Much of this newer understanding is a consequence of studies of the pharmaco-physiologic interactions of these agents in man and other animals, and to a considerable extent it has been stimulated by the post-war "drug explosion." The objective here is to review our current understanding of some of the newer concepts. To be covered are the renin-angiotensin system, mechanisms of drug action and some considerations that bear on who should be treated. These concepts must be looked upon as basic to the rational therapy of hypertension.

Renin-Angiotensin System

A significant development in recent years has been the conversion of our understanding of the renin-angiotensin system from speculation into fact. The enzyme renin is released from the juxta glomerular cells of the kidney in response to a fall in mean pressure or changes in sodium concentration in the ascending loop of Henle, or both.[39] In the blood it reacts with an alpha 2 globulin fraction (renin substrate) to form angiotensin I, a decapeptide. This inactive substance is converted to the active octapeptide, angiotensin II, by a converting enzyme in the plasma.[6,30] The most important action of angiotensin is stimulation of the adrenal to secrete aldosterone, which influences electrolyte and water shifts between the intracellular and extracellular spaces.

Renin has not been isolated, and all methods for assay of its activity involve reaction of the test sample with appropriate substrate for the pro-

---

Presented before the Section on Internal Medicine at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Department of Medicine, U.S. Public Health Service Hospital, 15th Avenue and Lake Street, San Francisco 94118.

duction of angiotensin II, the amount of which is reflected in vascular reactivity. This may be assessed by blood pressure response in rats or by the contractility of rabbit aorta strips.[5,15,27] All methods give qualitatively similar results, some of which are illustrated in Table 1.[43]

What useful clinical application can be made of this information?

The correlation of renin activity with the presence of correctable hypertension due to renal artery stenosis is reported to be excellent.[13] This correlation extends to split function tests, and to success or failure of surgical operations. It has remained high in unsuccessful revascularization procedures, and then fallen after subsequent nephrectomy.

Its most useful application at the moment, then, seems to be in the identification of subjects with hypertension due to renal artery stenosis, who are likely to be improved by correction.

It is also of interest that Conn and others have reported that 20 per cent of persons with so-called benign essential hypertension actually have primary aldosteronism, and that hypokalemia and alkalosis may not be evident for many years.[9] These subjects should have low to absent renin levels, since the normal feed-back mechanism should act to suppress renin secretion. Indeed, Helmer and others have found as many as 29 per cent of persons with benign essential hypertension have no detectable plasma renin activity.[14]

Do all such persons have aldosterone-producing adrenal adenomas? If so there may be several million potentially curable persons with hypertension throughout the country. Not only that, but since as many as 50 per cent of such patients may also have impaired carbohydrate tolerance, more than a million persons with so-called latent, chemical or maturity onset diabetes may also be curable.

TABLE 1.—*Serum Renin Activity Levels in Various States*

	High	*Normal*	*Low*
Renal artery stenosis (angio)	+	+	
Renal artery hypertension			
functional	+		
cured		+	+
Benign essential hypertension		+	+
Primary aldosteronism			+
Malignant hypertension	+		
Pregnancy	+		
Sodium depletion or diuretic use	+		
Coarctation		+	+
Primary renal parenchymal disease		+	+
Standing position	+		

Contemplation of these possibilities is a bit heady, and not surprisingly engenders great enthusiasm at many levels of medical endeavor. Unfortunately, this must be tempered with great patience and perhaps even a modicum of healthy skepticism. The laboratory tools for making these specific diagnoses are still investigational and may not become widely available to clinicians for some time. Nonetheless, the measurement of renin activity in plasma, and of the secretion of aldosterone by the adrenal glands, has opened the door on many exciting applications of our current understanding of the renin-angiotensin system.

Mechanisms of Drug Action

During the past decade new methods and concepts of biochemical pharmacology have greatly expanded our understanding of the role of the neurohormones, norepinephrine (NE) and epinephrine, as the effector agents of the sympathetic nervous system. Their influence extends not only to vascular smooth muscle, but also to heart, liver and adipose tissue. Much of this information stems from direct basic research on these catecholamines and their function in the body; some from studies of intermediary metabolism and factors influencing it; and some from fortuitous observations that certain drugs, used empirically in the treatment of hypertension, but which are totally unrelated structurally to the catechols, significantly influence or are influenced by catecholamine metabolism.

The role of the sympathetic nervous system in the complex regulatory mechanisms of the cardiovascular system, and the means by which certain pathologic states produce their effects, are also better understood, and in particular we are afforded an understanding of the mechanism of action of many of the newer antihypertensive agents. Norepinephrine is synthesized at the post ganglionic sympathetic nerve endings. The NE is stored in "granules" in a physiologically inert state.[41] It is in equilibrium with other NE in the nerve ending which is readily releasable either by nerve impulse or a drug such as tyramine (Chart 1). When released it interacts at a receptor site to produce an effect. Some of it may be metabolized to a less active compound for excretion, some undergoes re-binding in the nerve ending and some is washed out into the circulation, where it may be bound or metabolized in other tissues or excreted in the urine. In any event, by these means the interaction at the effector site is controlled and the area cleared of free NE until released again.[44]

Circulating NE is picked up and bound at the nerve endings, in addition to that which is synthesized there.[32] If not immediately released again, some of it may be transferred to the storage granules. In addition to transferring small amounts of its NE to the available pool, much of that in storage granules is deaminated by monomine oxidase into biologically inactive compounds which are excreted in that form or metabolized further to form vanilylmandelic acid (VMA).[23] Thus the tissue NE content is in a state of dynamic equilibrium. A certain amount is synthesized and/or taken up from the circulation, a smaller amount is released as free NE and the remainder is transformed by monomine oxidase and then released.

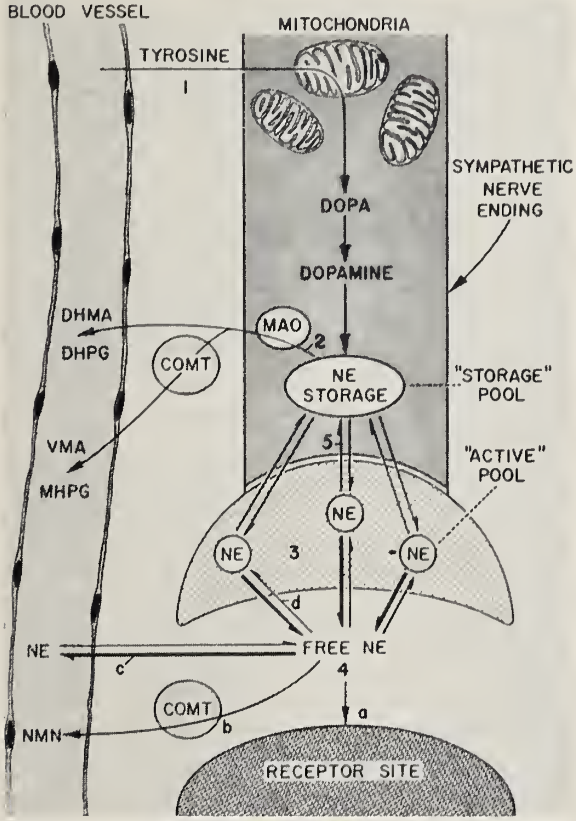


Chart 1.—Synthesis, storage, release and degradation interactions of norepinephrine at the sympathetic nerve ending.

1. Tyrosine is precursor for synthesis of norepinephrine (NE) via dopa and dopamine.

2. Storage NE is deaminated by monamine oxidase (MAO) and released as dihydroxymandelic acid (DHMA) or dihydroxyphenylglycol (DHPG) which may be metabolized to vanilylmandelic acid (VMA) or methoxyhydroxphenolglycol (MHPG) by catechol-O-methyl transferase (COMT).

3. Storage NE may be transferred to "active" pool of NE.

4. "Free" NE, either released from "active" pool or arriving via blood stream, may (a) interact at adrenergic receptor site, or (b) be metabolized to normetanephrine (NMN), or (c) be washed out into circulation or (d) undergo rebinding at the nerve ending.

5. Some NE bound in the "active" pool is transferred to the "storage pool."

It appears that sympathetic nerve endings release NE continuously, accounting for the observed circulating blood levels (0.3-0.4 nanogm* per ml). This level of secretion is partly independent of nervous impulses and in part the result of a basal level of neural activity.[7,16,40] Higher levels are noted following nerve stimulation, and of course the adrenal medulla releases norepinephrine in addition to epinephrine, mostly in spurts.

How, then, do the antihypertensive agents fit into this schema? Present understanding is as follows:

RESERPINE:

1. Reserpine depletes brain and sympathetic nerve endings of catecholamines. However, practically none of the central effect is responsible for the pressure lowering.[4,8]
2. In the peripheral nerve endings it has a direct releasing effect on the storage granules, both the deep and the easily releasable. Most of what it releases is deaminated; hence it rarely results in a paradoxical pressure rise.[23,24]
3. Since reserpine also blocks storage site uptake, most NE arriving in the circulation goes directly to effector sites, accounting for the so-called increased sensitivity to infused catecholamines.

GUANETHIDINE:

1. Depletes storage sites—primarily the active or readily releasable stores. It does so much faster than reserpine—usually in only three or four days.
2. Prevents release of NE in response to sympathetic nerve impulses.[17]
3. Blocks uptake by storage sites—therefore may also potentiate response to infused pressor catecholamines.

GANGLIONIC BLOCKERS:

1. Interfere with release of NE from sympathetic nerve endings by pre-ganglionic impul-

---

*One one-thousandth of a microgram.

ses, by blocking transmission through the ganglion.[16]

MONOAMINE OXIDASE (MAO) INHIBITORS

Pargyline:

1. Increases the stores of NE at the nerve endings by preventing the normal deamination of the deep stores by monoamine oxidase.[25]
2. Depresses the spontaneous release of NE from nerve endings, but not their release by tyramine.[2] This resultant build up of tyramine releasable NE in subjects taking MAO inhibitors, accounts for the reports of severe paradoxical hypertensive crises following the ingestion of cheddar cheese or chianti wine, each having a high tyramine content.[1,21,28]
3. In addition, in the presence of an MAO inhibitor, tyramine is metabolized to octopamine in the nerve ending and competes there with NE for storage sites. It can then be liberated as a "false transmitter," being many times less effective than NE at the receptor sites.[22,29]

A practical application of one bit of this information is a new diagnostic test for pheochromocytoma suggested by Engleman and Sjoerdsma.[12] The increased secretion of catecholamine from the tumor leads to increased amounts of readily releasable NE stores in the sympathetic nerve endings. When 1 mg of tyramine was injected intravenously, persons with such tumors had a rise in blood pressure of over 20 mm of mercury, while normal persons or those with essential hypertension did not have rises exceeding 5 mm of mercury.

DECARBOXYLASE INHIBITORS: *Alpha methyl dopa* (AMD)

Not long after AMD was in clinical trial it was demonstrated that its pressure-lowering effect was dissociable from its enzyme inhibition.[33] Hence it does *not* have its effect through decreasing synthesis of NE. Indeed, no anti-hypertensive agent studied to date has this mechanism of action.

It is now known that AMD, like MAO inhibitors, has its effect via the "false transmitter mechanism.[11]" In fact it is itself decarboxylated and metabolized to alpha methyl dopamine or alpha methyl norepinephrine, which are able to compete successfuly with NE for storage sites. They are then either poorly released or are less potent effectors, or both.

Finally, then, it is now understood why such drugs as imipramine and chlorpromazine, which are neither NE depletors nor involved with false transmitter production, are not infrequently associated with hypotensive reactions. Both are known to behave like cocaine and block the uptake and binding of NE at the nerve endings.[18,42] As with reserpine and guanethedine, the effects of secreted or injected catecholamines may be enhanced and prolonged. Chlorpromazine also blocks alpha receptors directly and may act centrally as well.

Hydralazine

The mechanism of action of this drug is unknown. However, certain of its effects suggest that it may act directly to block the alpha adrenergic receptors and stimulate the beta adrenergic receptors.[3] This would be consistent with its observed effect of reducing peripheral resistance while at the same time increasing cardiac output, heart rate and renal blood flow. It would also be consistent with its known ability to block the pressor effects of angiotensin and norepinephrine which act directly on the receptor sites.

Chlorothiazide

The mechanism of action of clorothiazide also remains to be established. The diuretic and saluretic effect with the initial fall in plasma volume and cardiac output can be dissociated from the long-term pressure-lowering effect.[10,19] This is accomplished merely by continued administration, or by modification of the molecule as in the case of its analogue, diazoxide. It appears now that the thiazides reduce the blood pressure by reducing peripheral resistance. Whether this is accomplished by altering the distribution of water and electrolytes in the vessel wall or by reducing their catecholamine content is not established.[20,38]

Selection of Cases for Therapy

It has been adequately demonstrated that lowering of blood pressure with drugs in persons with severe or malignant hypertension, strikingly increases their survival.[26,31,34,35] It has not been established that the same is true for the benign, mild to moderate phase of the disease, nor has it been proven that the level of arterial pressure is the major factor in the development of the classic complications.

However, in view of (1) the observed good results in therapy of the malignant phase, (2) the awesome excess morbidity and mortality of persons with untreated benign hypertension as compared with blood pressure in normal range,[36,37] and (3) the fall in incidence of severe and malignant cases in the years since the wide-spread us of effective drugs began—in view of these phenomena, I believe that with the exception of investigators in the process of obtaining objective evidence to support or refute this premise, we are justified in proposing that all persons with mild and moderate disease be treated, or at least managed. For this purpose the following definitions are employed:

Hypertensive disease — blood pressure 160/100 mm of mercury and over. (All persons with blood pressure of this range should have a complete evaluation followed by appropriate treatment).

Severe—(1) Moderate pressures (160/100 to 200/120 mm of mercury) plus complications such as congestive heart failure, cerebrovascular accident, retinopathy greater than grade II, azotemia, or (2) Sustained pressures greater than 200/100 mm of mercury.

Moderate—160/100 to 200/120 mm of mercury without complications other than left ventricular hypertrophy as demonstrated by electrocardiogram or x-ray study.

Borderline—Includes both mild and labile cases, which are defined as follows:

Mild—140/90 to 160/100 mm of mercury without complications and with or without symptoms. (We are currently treating these patients and find that nearly all are rendered normotensive with thiazide diuretics, sometimes supplemented by a rauwolfia preparation.)

Labile—Hypertension noted on three clinic visits but diastolic pressure at home averages less than 90 mm of mercury. (If patient is asymptomatic, no drug therapy is given unless required for employment. If there are mild symptoms in a tense, nervous patient, they may be treated with sedatives or rauwolfia. In a few years we may find that all of these patients should be treated. In the meantime, they should all be observed regularly, and this may be "management" enough).

REFERENCES

1. Asatoor, A. M., Levi, A. J., and Milne, M. D.: Tranylcypromine and cheese, Lancet, 2:733, 1963.

2. Axelrod, J., Hertting, G., and Patrick, R. W.: Inhibition of H_3-norepinephrine release by monoamine oxidase inhibitors, J. Pharmacol. Exp. Ther., 134:325-328, 1961.

3. Barret, W. E., Povalski, H., and Rutledge, R.: A hypothesis concerning the mechanism of action of hydralazine HG1, Fed. Proc., 24:712, 1965.

4. Bertler, A., Carlsson, A., and Rosengren, E.: Release by reserpine of catecholamines from rabbit's heart, Naturwissenschaften, 43:521, 1956.

5. Boucher, R., Veyrat, R., de Champlain, J., and Genest, J.: New procedures for the measurement of human plasma angiotensin and renin levels, Canad. Med. Assn. J., 90:194, 1964.

6. Braun-Mendez, E.: Pharmacology of renin and hypertension, Pharmacol. Rev., 8:25, 1956.

7. Braunwald, E., Harrison, D. C., and Chidsey, C. D.: Heart as endocrine organ, Amer. J. Med., 36:1-4, 1964.

8. Clementi, F., and Zocche, G. P.: Morphological and pharmacological effects of reserpine, given alone or after iproniazid, on catecholamines of adrenal glands of rat, J. Cell. Biol., 17:587-596, 1963.

9. Conn, J. W., Cohen, E. L., Rovner, D. R., Nesbit, R. M.: Nomokalemic primary aldosteronism, J.A.M.A., 193:200-206, 19 July 1965.

10. Conway, J., and Lauwers, P.: Hemodynamic and hypotensive effects of long-term therapy with chlorothiazide, Circulation, 21:21, 1960.

11. Day, M. D., and Rand, M. J.: Hypothesis for mode of action of a-methyldopa in relieving hypertension, J. Pharm. Pharmacol., 15:221-224, 1963.

12. Engelman, K., and Sjoerdsma, A.: New test for pheochromocytoma—Pressor responsiveness to tyramine, J.A.M.A., 189:71-86, 1964.

13. Gunnells, J. Caubie: Application of a renin assay in evaluation of hypertension, council for high blood pressure research, Amer. Heart Assn., Bal Harbour, Florida, October 1965.

14. Helmer, O. M.: The renin-angiotensin system and its relation to hypertension, Progr. Cardiovasc. Dis., 8:117-128, September 1965.

15. Helmer, O. M., and Judson, W. E.: The quantitative determination of renin in the plasma of patients with arterial hypertension, Circulation, 28:1050, 1963.

16. Hertting, G., Potter, L. T., and Axelrod, J.: Effect of decentralization and ganglionic blocking agents on spontaneous release of H_3-norepinephrine, J. Pharmacol. Exp. Ther., 136:289-292, 1962.

17. Hertting, G., Axelrod, J., and Patrick, R. W.: Actions of bretylium and guanethidine on uptake and release of H_3-noradrenaline, Brit. J. Pharmacol., 18:161-166, 1962.

18. Hertting, G., Axelrod, J., and Whitby, L. G.: Effect of drugs on uptake and metabolism of H_3-norepinephrine, J. Pharmacol. Exp. Ther., 134:146-157, 1961.

19. Hollander, W., Chobanian, A. F., and Wilkins, R. W.: Relationship between diuretic and antihypertensive effects of chlorothiazide and mercurial diuretics, Circulation, 19:827, 1959.

20. Hollander, W., Yagi, S., and Kramsch, D. M.: In vitro effects of vasopressor agents on the metabolism of the vascular wall, Circulation (Suppl. II), 1964.

21. Horwitz, D., Lovenbert, W., Engelman, K., and Sjoerdsma, A.: Monoamine oxidase inhibitors, tyramine, and cheese, J.A.M.A., 188:1108-1110, 1964.

22. Kopin, I. J., Fisher, J. E., Musacchio, J., and Horsh, W. O.: Evidence for false neurochemical transmitter as mechanism for hypotensive action of monoamine oxidase inhibitors, Proc. Nat. Acad. Sci., 52:716-721, 1964.

23. Kopin, I. J., Hertting, G., and Gordon, E. K.:

Fate of norepinephrine-H_3 in isolated perfused heart, J. Pharmacol. Exp. Ther., 138:34-40, 1962.

24. Kopin, I. J., and Gordon, E. K.: Metabolism of norepinephrine-H_3 released by tyramine and reserpine, J. Pharmacol. Exp. Ther., 138:351-359, 1962.

25. Kopin, I. J.: Storage and metabolism of catecholamines—Role of monoamine oxidase, Pharmacol. Rev., 16:179-191, 1964.

26. Leishman, A. W. D.: Merits of reducing high blood-pressure, Lance, 1:1284, 1963.

27. Lever, A. F., Robertson, J. I. S., and Tree, M.: The estimation of renin by an enzyme kinetic technique, Biochem. J., 91:346, 1964.

28. McClure, J. L.: Reactions associated with tranylcypromine, Lancet, 1:1351, 1962.

29. Musacchio, J., Fischer, J. E., and Kopin, I. J.: Effect of chronic sympathetic denervation on subcellular distribution of some sympathomimetic amines, Biochem. Pharmacol., 14:898-900, 1965.

30. Page, I. H., and Bumpus, F. M.: Angiotensin, Physiol. Rev., 41:331, 1961.

31. Perry, H. M., Jr., and Schroeder, H. A.: Studies on the control of hypertension. VIII. Effects of ganglionic blockade combined with hydralazine on the malignant stage complicated by renal azotemia, Circulation, 14:105, 1956.

32. Potter, L. T., and Axelrod, J.: Subcellular localization of catecholamines in tissue of rat, J. Pharmacol. Exp. Ther., 142:291-298, 1963.

33. Sjoerdama, A., Vendsaln, A., Engleman, K.: Studies on the metabolism and mechanism of action of methyldopa, Circulation, 28:492-502, October 1963.

34. Smirk, F. H., Hamilton, M., Doyle, A. E., and McQueen, E. G.: The treatment of hypertensive cardiac overload by blood pressure reduction, Amer. J. Cardiol., 1:143, 1958.

35. Smirk, F. H.: Observations on the mortality of 270 treated and 199 untreated retinal grade I and II hypertensive patients followed in all instances for five years, New Zealand Med. J., 63:413, 1964.

36. Society of Actuaries: Build and blood pressure study, 1, Chicago, 1959.

37. Sokolow, M., and Sanazaro, P. J.: Cardiovascular disease: Arterial hypertension, Ann. Rev. Med., 11:59, 1960.

38. Tobian, L., Jr.: The Relationship of Sodium to Hypertension (Clinical Observations). From Hypertension—Recent Advances, Edited by A. N. Brest and J. H. Moyer, Lea & Febiger, Philadelphia, 1961, p. 90.

39. Tobian, L.: Interrelationship of electrolytes, juxtaglomerular cells and hypertension, Physiol. Rev., 40:280, 1960.

40. von Euler, U. S.: Adrenergic Neurohormones, From Comparative Endocrinology. Edited by U. S. von Euler and H. Heller, Academic Press, New York, 1963, pp. 258-290.

41. von Euler, U. S., and Hillarp, N. A.: Evidence for presence of noradrenaline in submicroscopic structure of adrenergic neurons, Nature (London), 177:44, 1956.

42. Whitby, L. G., Hertting, G., and Axelrod, J.: Effect of cocaine on disposition of noradrenaline labelled with tritium, Nature (London), 187:604, 1960.

43. Winer, Bertram: Renin Secretion, Council for High Blood Pressure Research, Amer. Heart Assn., Bal Harbour, Florida, October 1965.

44. Wurtman, R. J.: Catecholamines, New Engl. J. Med., 273:637-646, 16 September 1965.

CASE REPORTS

Gastrointestinal Hemorrhage Due to Rupture of an Aortic Homograft

ALEX GERBER, M.D., AND
NORMAN RUBAUM, M.D., *Alhambra*

GASTROINTESTINAL HEMORRHAGE due to the rupture of an abdominal aortic homograft or synthetic prosthesis is now a well recognized entity. In the case presented here there were two distinguishing features: Rupture of an aortic homograft seven years after its insertion, and the presence of blood in the stomach from bleeding into the distal ileum. Had we been alerted to this latter possibility, a fatal outcome in this case might have been averted.

DeWeese and Fry[3] summarized 40 cases of aortic replacement grafts, complicated by late rupture into the intestinal tract, reported to 1962 and added reports of four such complications of their own. They credited Brock (1953) with the first report of the rupture of an aortic homograft into the duodenum. In the cases reviewed by DeWeese and Fry, only two of the perforations were located in the ileum; the duodenum and jejunum were the sites of the remainder.

Clayton and coworkers[1] described a rupture of a nylon aortic graft into the distal ileum. In this instance, the bleeding was manifested by bright red blood from the rectum and the patient died of exsanguination. Hagland, Sweetman, and Wise[4] reported a rupture of a homograft into the midileum, and the patient in that case also bled per rectum.

Harrison[5] correctly predicted, on the basis of animal experiments, that there would be a greater incidence of late complications and breakdowns with aortic homografts than with synthetic grafts. DeWeese and Fry have pointed out that the mechanism of perforation and bleeding differs, depending upon the type of graft. These investigators noted that synthetic grafts act as foreign bodies, causing erosion of adjacent intestine when not protected by intervening tissue. They expressed belief that the resultant infection predisposes to a disruption of the suture line of the graft and intestinal hemorrhage, usually within a few days to a few months after aortic grafting. On the other hand, they noted that aortic homografts may gradually weaken and undergo aneurysmal dilatation after months or years. It is this new aneurysm, they said, which ruptures into the intestinal tract.

Report of a Case

A 74-year-old man entered the hospital on 14 January 1965, with a complaint of faintness and the passage of bright red blood per rectum for the previous three hours. There was no history of pain or of any other symptoms usually associated with a peptic ulcer, cirrhosis of the liver or disease of the colon.

In October of 1957, the patient had had resection of an abdominal aortic aneurysm by one of us (A.G.) with bifurcation homograft replacement. Convalescence was uneventful, and the patient remained asymptomatic until immediately preceding the present admission.

Upon admission, the systolic blood pressure was 130 mm of mercury and the pulse rate was 96. The skin was cool and dry. No abnormality was noted on abdominal examination. Fresh blood was

---

Submitted 17 May 1966.

Reprint requests to: Alhambra Medical Clinic, 1237 East Main Street, Alhambra 91801 (Dr. Gerber).

found in the rectum and sigmoid by digital and sigmoidoscopic examination. Hemoglobin was 13.2 gm per 100 ml of blood and the hematocrit was 37.

The blood pressure dropped and the patient became cold and clammy intermittently in the next 18 hours. During this time, a total of 5,500 ml of blood was administered and there was prompt reversal of the symptoms of shock after each transfusion of 500 to 1,000 ml. The urinary output was 50 to 90 ml per hour during this period.

Twelve hours after admission, bright red blood appeared in the nasogastric suction tube. Until that time, all bleeding had been from the rectum. The patient was taken to the operating room with a diagnosis of upper gastrointestinal tract hemorrhage on the basis of the appearance of blood in the stomach.

At operation, the entire gastrointestinal tract was seen to be filled with fresh blood. The lower esophagus, stomach, duodenum, and upper jejunum were thoroughly investigated through multiple gastroenterotomy incisions in a futile effort to find the source of the bleeding. Openings were made at intervals along the intestine and a sterile sigmoidoscope was used to visualize the portions between the openings. A good deal of time was consumed in these maneuvers before the source of the bleeding was discovered in the distal ileum —a 2 cm aneurysm of the right iliac branch of the homograft that had ruptured into the intestine. The homograft was excised and replaced with a synthetic graft.

The patient was in shock during much of the operation despite the intravenous administration of 5,000 ml of blood. He died five hours postoperatively.

Discussion

The complication of rupture of an aortic aneurysm into the intestinal tract is well recognized. Interestingly, the rupture and the severity of the bleeding is not related to the size of the aneurysm. An important diagnostic feature of this type of bleeding is absence of the usual symptoms and signs associated with the common causes of gastrointestinal hemorrhage, such as peptic ulcer and esophageal varices. (In the present case no abdominal mass could be felt, since the aneurysmal dilatation measured only 2 cm.) Moreover, since the aortic rupture is into the intestine, there is no telltale retroperitoneal hematoma to alert the surgeon at the operating table to the disruption of a large vessel. Other observers[2,4] have commented on the ease of missing an aortico-intestinal fistula.

The appearance of bright red blood in the stomach in the present case should be stressed. It is commonly believed that this finding is pathognomic of bleeding proximal to the ligament of Treitz. Because we adhered to this belief, a good deal of time was consumed in meticulous examination of the esophagus, stomach and duodenum for the source of the hemorrhage. Obviously, in rare instances massive bleeding from the distal small intestine will manifest itself by the blood in the stomach.

Finally, we call attention to the time interval between the insertion of the homograft and its rupture into the intestine. The seven-year period reported here is the longest recorded in the literature. It is well to know that aneurysmal dilatation of homografts may occur after prolonged asymptomatic function of such grafts. Since all of the early replacement procedures for the treatment of aortic aneurysms were performed with homografts rather than the synthetics, many more surgical emergencies of the type here reported can be anticipated.

Summary

A patient with rupture of an abdominal aortic homograft into the distal ileum seven years after the graft was placed is presented. The mechanism and diagnostic feature of rupture of homografts and synthetic grafts are discussed. Particular attention is called to the possibility of finding bright red blood in the stomach when the source of the hemorrhage is in the distal small intestine and to the long asymptomatic interval between insertion and rupture of the homograft in the patient reported.

REFERENCES

1. Clayton, H., Birtch, L., Cardwell, E. S., and Zimmerman, S. L.: Suture-line rupture of a nylon aortic bifurcation graft into the small bowel, Arch. Surg., 73: 947, Dec. 1956.

2. Cordell, A. R., Wright, R. H., and Johnston, F. R.: Gastrointestinal hemorrhage after abdominal aortic operations, Surgery 48:997, 1960.

3. DeWeese, M. D., and Fry, W. J.: Small-bowel erosion following aortic resection, J.A.M.A., 179:882, 1962.

4. Hagland, L. A., Sweetman, W. R., and Wise, R. A.: Rupture of an abdominal aortic homograft with ileal fistula, Am. J. Surg., 98:746, 1959.

5. Harrison, J. A.: Influence of infection on homografts and synthetic grafts, Arch. Surg., 76:67, 1958.

Primary Duodenal Carcinoma Antedated By a Benign Adenomatous Polyp

EDWIN S. WILSON, JR., CAPTAIN, MC, USA, AND
JAMES J. DU BOIS, LT. COLONEL, MC, USA,
San Francisco

PRIMARY CARCINOMA of the duodenum is an uncommon neoplasm. In a review of 117,433 post mortem examinations, Howard[5] established that the incidence of duodenal carcinoma in this group was 0.04 per cent. This figure is in general agreement with the incidence of 0.033 per cent cited by Hoffman and Pack[4] in 350,286 cases at autopsy. Although they are the most common of small bowel benign tumors, adenomatous polyps are also uncommon, and Bockus[1] placed the incidence of small intestinal benign neoplasms at 0.16 per cent. The present report concerns the development of a primary duodenal carcinoma 11 years after duodenal polypectomy and explores the possible relationship between these lesions.

Case Report

A 49-year-old man was well until 1953 when symptoms suggestive of peptic ulcer disease developed. An active ulcer crater was demonstrated roentgenographically in the duodenal bulb. A 1.5 cm pedunculated polyp was incidentally noted in the second portion of the duodenum, with the stalk originating in the region of the ampulla of Vater (Figure 1). In July 1953 the polyp was removed. On histologic examination, adenomatous mucosal proliferation consistent with the diagnosis of benign adenomatous polyp was noted.

The patient then was asymptomatic until June 1964 when he was admitted to hospital for gastrointestinal bleeding, requiring replacement of 2,000 ml of blood. An upper gastrointestinal series demonstrated a deformed duodenal bulb, as well as deformity and mucosal irregularity in the descending duodenum (Figure 2) considered secondary

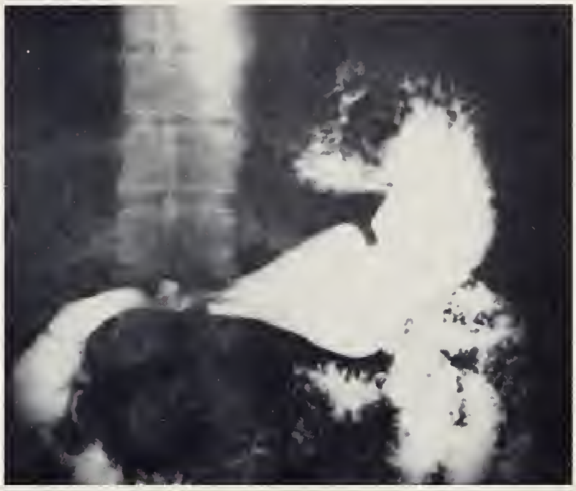


Figure 1.—Part of upper gastrointestinal series in 1953 demonstrating ulcer crater within the duodenal bulb and pedunculated polyp in the descending portion of the duodenum.

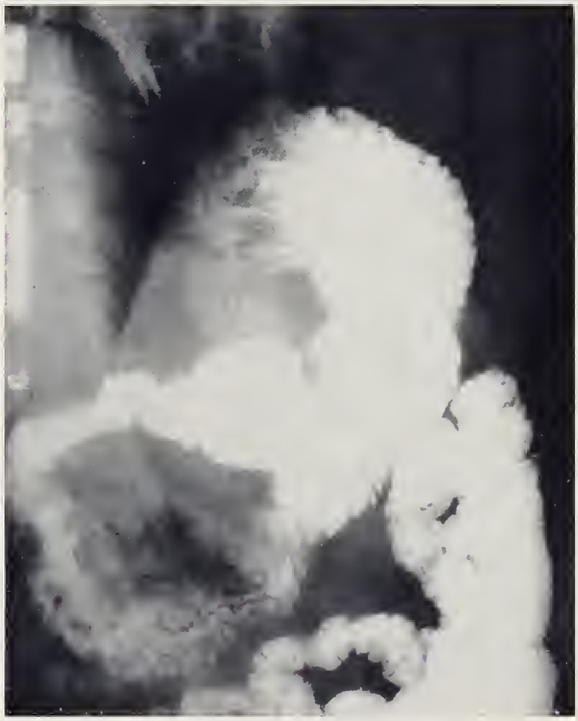


Figure 2.—From upper gastrointestinal series in 1964 demonstrating an irregular infiltrating lesion in the descending portion of the duodenum.

From the Department of Radiology, Letterman General Hospital, San Francisco.

This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

Submitted 7 June 1966.

Reprint requests to: Radiology Department, Letterman General Hospital, San Francisco 94129 (Captain Edwin S. Wilson, Jr.).

to the duodenal polypectomy performed in 1953. The patient was discharged.

In September he was readmitted with melena. Chills, fever and jaundice developed and the stools became light in color. A gastrointestinal radiographic examination showed the deforming duodenal lesion to be unchanged in appearance. A duodenal aspiration was negative for malignant cells. An attempt to obtain a biopsy specimen from the small bowel was unsuccessful because the capsule could not be passed beyond the constricting lesion. A percutaneous transhepatic cholangiogram demonstrated an obstructive lesion of the distal 2 cm of the common bile duct with an eccentric smooth filling defect on its superior aspect, believed to be consistent with neoplasm (Figure 3).

An exploratory operation confirmed the presence of an annular filling defect in the second portion of the duodenum. On frozen section examination it was interpreted as adenocarcinoma. A radical Whipple procedure was performed, and permanent sections confirmed the diagnosis of primary duodenal carcinoma. At last report, a year after operation, the patient was free of symptoms.

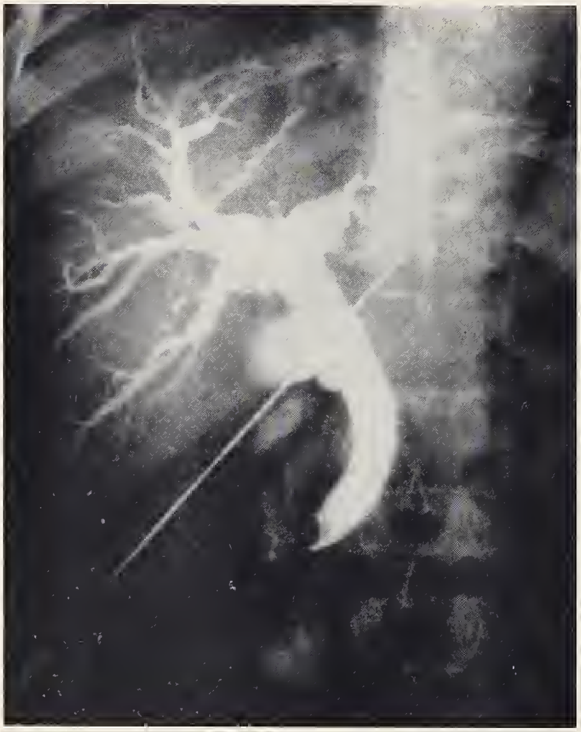


Figure 3.—Percutaneous transhepatic cholangiogram demonstrating duct dilatation and the smooth filling defect at the site of obstruction. Some contrast material has passed through this area into the duodenum.

Discussion

Adenomatous polyps occur more often in the ileum than in the duodenum and more often in the duodenum than in the jejunum. The region of the ampulla of Vater in the duodenum appears to be a favorite location for the tumor, and the lesion may be sessile or pedunculated. Although opinion is divided as to the malignant potential of polyps of the small bowel, there does not appear to be definite evidence that these tumors are precancerous. Duodenal carcinoma occurring in the Peutz-Jeghers syndrome has been reported; however, the polyps of this syndrome appear to be a rather characteristic type, and it has been proposed that these lesions are hamartomas.[8,10]

The descending portion of the duodenum appears to undergo malignant change more frequently than other portions. Of the primary duodenal carcinomas 22.5 per cent are supra-ampullary, 59.2 per cent are peri-ampullary, and 18.3 per cent are infra-ampullary.[6] The majority of duodenal malignant lesions are of the cylindrical-cell variety of adenocarcinoma of mucosal origin, although rarer types of carcinoma may arise from heterotopic gastric or pancreatic tissue or from Brunner's gland elements. Metastasis usually occurs late in the course of the disease, with spread most commonly to regional nodes. It is estimated that in 30 per cent of peri-ampullary and 60 per cent of infra-ampullary carcinomas, distant metastasis is found at the time of autopsy, usually to liver and lung.[9]

The etiologic lineage of duodenal carcinoma is unknown, but several interesting theories have been advanced.[3,4,5] The ampulla of Vater is the junction of two types of epithelium and it has been suggested that interplay between the two might be a factor in the apparent tendency for malignant degeneration in this portion of the duodenum. A theory proposed by Geiser emphasizes the factor of chronic irritation by the duodenal contents and by digestive enzymes upon the mucosal cells. Certainly the present case exemplifies the proclivity of the descending portion of the duodenum to be involved by both benign polyps and malignant adenocarcinoma, and recalls the as yet unanswered questions of etiology and possible pathogenic relationship between these two entities.

The clinical manifestations reflect to a certain extent the anatomic location of the lesions. The symptom complex associated with benign polyps is vague and insidious, and as many as 50 per cent of these lesions may be totally asymptomatic. The early symptoms of duodenal malignant disease are also vague; they include pain, anorexia, fatigue and loss of weight. Later symptoms and signs include gastrointestinal bleeding, epigastric or right upper quadrant pain, palpable mass, jaundice and obstruction. The jaundice is characteristically intermittent, and this is thought to be related to periodic sloughing of the superficial portions of a peri-ampullary tumor.[4] If penetration occurs, the pain becomes "boring" in quality and often radiates to the back.

The radiographic characteristics relate to the findings on upper gastrointestinal series and the somewhat more specialized roentgenographic procedure of percutaneous transhepatic cholangiography*:

- The lesion may be annular or infiltrating, with or without areas of ulceration. Irregular polypoid defects may also be seen less commonly.
- The mucosal pattern is disrupted, with thickening and effacement of folds, and the involved segment is relatively rigid with disturbed peristaltic activity.
- Dilatation of the duodenum and stomach proximal to the lesion may occur. This may produce gastric retention.
- In peri-ampullary lesions with biliary obstruction, the impression of a dilated common duct may be seen in the region of the junction of the first and second portions of the duodenum.
- In the presence of biliary obstruction the percutaneous transhepatic cholangiogram demonstrates dilatation of the common duct and hepatic ducts, with a rather characteristic appearance at the site of obstruction. This finding is either a saw-tooth margin at the level of the obstruction or a smooth margin with a meniscus projecting into the lumen. The latter pattern was demonstrated in the present case.

The natural course of untreated duodenal malignant disease is usually death within one year, and the cause of death may be prolonged biliary obstruction with its sequelae—hemorrhage, or perforation and peritonitis. In cases in which the lesions are resectable, the five-year survival average is approximately 6 to 12 per cent.[11]

---

*Reference Nos. 1, 2, 4, 6, 7, 9.

Summary

This report is of a patient with primary duodenal carcinoma who had had a benign adenomatous polyp removed from the same site. The pertinent clinical and radiographic findings are presented.

REFERENCES

1. Bockus, H. L.: Gastroenterology, Vol. II, Second Ed., W. B. Saunders Company, Philadelphia and London, 1964.
2. Evans, John A: Techniques in the detection and diagnosis of malignant lesions of the liver, spleen, and pancreas, Radiologic Clinics of North America, 3:567-582, 1965.
3. Geiser, J. F.: Beitrage zur Geschwulstlehre. II. Uber Duodenalkrebs, Deutsch. Ztschr. f. Chir., 86:41-107, 1907.
4. Hoffman, W. J., and Pack, G. T.: Cancer of the duodenum; clinical and roentgenographic study of 18 cases, Arch. Surg., 35:11-63, 1937.
5. Howard, John W.: Carcinoma of the duodenum, Amer. Jour. Med. Sci., 206:735-746, 1943.
6. Kleinerman, J., Yarduman, K., and Tamaki, H. J.: Primary carcinoma of the duodenum, Ann. Int. Med., 32:45-465, 1950.
7. Kline, J. R., and Culver, G. J.: Roentgen findings in primary duodenal and paraduodenal malignant lesions, Am. J. Roent-Genol., Rad. Ther. & Nuclear Med., 58: 425-438, 1947.
8. Morson, G. C.: Precancerous lesions of the upper gastrointestinal tract, J.A.M.A., 179:311-315, 1962.
9. Palmer, Eddy D.: Clinical Gastroenterology, Second Ed., Hoeber Medical Division, Harper and Row Publishers, New York, 1963.
10. Reid, J. D.: Duodenal carcinoma in the Peutz-Jeghers syndrome, Cancer, 970-977, 1965.
11. Sheehy, Thomas W., and Floch, Martin H.: The Small Intestine: Its Function and Diseases, Hoeber Medical Division, Harper and Row Publishers, New York, 1964.

Retroperitoneal Hematoma Following Retroperitoneal Pneumography

PAUL S. MAHONEY, M.D., *San Fernando*

RETROPERITONEAL PNEUMOGRAPHY, introduced by Carelli[2] in 1921, has become a popular radiographic technique for visualizing the adrenal glands. The earliest investigators, including Cahill[1] and Rivas[5] used ordinary air. As the procedure gained more widespread recognition, however, complications were encountered. The dan-

---

From the Department of Radiology, Center for the Health Sciences, University of California, Los Angeles.

Submitted 18 May 1966.

Reprint requests to: Holy Cross Hospital, 15031 Rinaldi Street, San Fernando 91340.

gers inherent in the procedure were recognized and investigators turned to the use of oxygen and carbon dioxide.

The major complication, air embolism, has been extensively discussed in the literature. Minor complications fall into four general categories: Emphysema of the cervical, mediastinal and scrotal areas; infections of the perirectal and retroperitoneal spaces; pain in the abdomen, flank and chest; and pneumothorax.

Air embolism has been encountered so often that the procedure is eschewed unless there are precise indications for it.

The first fatality was reported by Weyrauch[7] in 1940, and others followed.[8,9] More recently, an extensive survey by Ransom, Landes and McLelland[4] turned up reports of 58 deaths and 64 severe non-fatal reactions. On the other hand, Steinbach and Smith[6] reported a survey of 1,999 cases in which the procedure had been carried out without serious reaction.

In the case here reported a retroperitoneal hematoma developed following retroperitoneal pneumography, a complication believed not to have been reported previously.

Report of a Case

A 41-year-old woman entered the hospital with complaint of flushing spells, pain and burning on the right side of the neck and shoulder, numbness in the extremities, intermittent loss of visual acuity, and occasional morning nausea.

On physical examination she appeared to be in no distress. Blood pressure was 126/78 mm of mercury and the pulse rate was 72 and regular. There appeared to be a tender right mid-abdominal mass which, upon pressure, caused a flushing of the neck and face of the patient, the flush lasting approximately 15 or 20 minutes. Concomitantly the blood pressure became elevated to the range of 150/90 mm. Results of cold pressor, histamine and vanilloylmandelic acid tests were negative. The 17-ketosteroid values were within normal range.

An intravenous pyelogram, barium enema studies and upper gastrointestinal series showed no abnormality.

The attending physician included pheochromocytoma and carcinoid tumor in the differential diagnosis. Since the initial barium studies revealed no evidence of a carcinoid tumor, retroperitoneal pneumography was done to evaluate the adrenal glands. Nitrous oxide in a volume of 1,600 ml was introduced into the presacral region. The patient tolerated the procedure well, adequate roentgenograms were obtained, and the adrenal glands were found to be normal.

The patient was subsequently discharged from the hospital. Two weeks later, she noticed insidious onset of pain in the left lower quadrant of the abdomen. On examination a firm, non-pulsatile mass about 10 cm in diameter was felt in the left lower quadrant of the abdomen. No bruit was heard. No abnormalities were noted on pelvic examination. Roentgenographic examination of the abdomen showed a homogenous, expanding radiodensity in the left retroperitoneal area, effacing the left psoas contour in its mid-portion and the lower pole of the left kidney.

At operation a large encysted hematoma was found in the retroperitoneal region on the left side, extending from the left mid-abdomen into the left iliac fossa. The hematoma was evacuated and drains were inserted. The patient recovered promptly.

Pathological examination of the specimen showed it to be an organizing hematoma with pseudocapsular formation.

Summary

A case of a retroperitoneal hemorrhage complicating retroperitoneal pneumography is reported. It is believed to be the first reported complication of this kind associated with this procedure.

REFERENCES

1. Cahill, G. F.: Air injections to demonstrate adrenals by x-ray, J. Urol., 34:238, 1935.
2. Carelli, H. H.: Artificial emphysema for roentgenography of the kidney, Bull. Soc. med hop. Paris, 45: 1409, 1921.
3. Glassman, I., Shapiro, R., and Robinson, F.: Air embolism during presacral pneumography, J. Urol., 75: 569, 1956.
4. Ransom, C. L., Landes, R. R., and McClelland, R.: Air embolism following retroperitoneal pneumography: A nation-wide survey, J. Urol., 76:664, 1956.
5. Rivas, M. R.: Roentgenological diagnosis, generalized subserous emphysema through a single puncture, Am. J. Roentgenol., 64:723, 1950.
6. Steinbach, H. L., and Smith, D. L.: Extraperitoneal pneumography in diagnosis of retroperitoneal tumors, A. M. Ass. Arch. Surg., 10:161, 1955.
7. Weyrauch, H. M., Jr.: Death from air embolism following perirenal insufflation, J.A.M.A., 114:652, 1940.
8. Wilhelm, S. F.: Gas insufflation through the lumbar and presacral routes, Surg. Gynec. & Obst., 99:319, 1954.
9. Year Book of Urology 1953-1954 Series, W. W. Scott, editors, comment p. 32. Year Book Publishers, Chicago, 1955.

MEDICAL STAFF CONFERENCE

Vitamin D Resistant Rickets

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. THOMAS A. LOVE*: This is the second admission to hospital of a 5-year-old caucasian boy who was admitted for evaluation of bone disease. At birth he appeared entirely normal and weighed six pounds, seven ounces. Pregnancy had been uncomplicated as was delivery and the first year of the patient's life. His diet was supplemented throughout this period with a multiple vitamin preparation, dose unknown.

The patient began walking at the age of one year and within three months some bowing of his legs was noted by the mother. Shortly thereafter prominence of the patient's forehead prompted the mother to seek medical attention. X-ray films of the skull at this time demonstrated closure of the sutures and some synostosis. Films of the femurs were said to show evidence of rickets. Because of these findings he was admitted to the hospital, where studies showed persistent hypophosphatemia but normal levels of serum calcium and alkaline phosphatase.

A diagnosis of vitamin D resistant rickets was made and vitamin D therapy was begun with 50,000 to 100,000 units intravenously on alternating days. Despite this therapy, hypophosphatemia persisted and growth retardation was noted. Between the ages of three and five the height and weight remained below the fifth percentile. For these reasons, the patient was readmitted.

On physicial examination he appeared alert. Vital signs were normal. He was noted to have a slight pectus excavatum deformity of the chest. No rachitic rosary was observed. There was slight flaring and widening of both wrists but no bone tenderness. He had short, thickened fingers, and very mild bowing of the proximal femurs. The remainder of the physical examination was within normal limits.

Laboratory studies are summarized in Table 1.

Following admission, the patient was placed on a low phosphorus diet and vitamin D 50,000 units and 100,000 units by mouth on alternating days. On this program the patient's urine calcium was 134 mg per 24 hours, urine phosphorus was 442 mg per 24 hours, and tubular reabsorption of phosphate was 63 per cent (normal, greater than 76 per cent).

During the stay in hospital, viral pneumonitis developed in the left lower lobe. It cleared rapidly.

TABLE 1.—*Laboratory Data*

Hemoglobin—12.8 gm per 100 ml
Leukocyte blood cell count—7,000 per cu mm
Carbon dioxide—21.3 mEq per liter
Calcium—9.4 mg per 100 ml
Phosphorus—2.4 mg per 100 ml
Creatinine—0.8 mg per 100 ml
Alkaline phosphatase—10.5 Shinowara-Jones-Reinhart Units (normal 2 to 6 SJR units)
Serum carotene—0.12 mg per 100 ml (normal 0.05-0.30)
Urinalysis—within normal limits
Sulkowitch test—negative

---

*Intern in Medicine.

Dr. Howard L. Steinbach[*1]: X-ray examination of the knees when the patient was three years old demonstrated evidence of rickets which consisted primarily of a thickening of the epiphyseal cartilage, more obvious medially. Similar thickening of the cartilage of the proximal end of the tibia was also seen. Normally a white line crosses the end of the metaphysis which is a zone of provisional calcification. In this patient, a slight line indicated that the cartilage was growing but was not properly calcified. The distal end of both femurs was curved, a finding characteristic of rickets. One of the characteristics of vitamin D resistant rickets is increased density of the bones. This finding when present distinguishes patients with vitamin D resistant rickets from patients with dietary rickets, in whom the bones are demineralized. The bones in this patient were not only overly dense but were also too thick.

Bone changes are best seen about the knees in vitamin D resistant rickets. In this patient, there was no evidence of rickets about the hips, and the wrists were relatively normal. A film of the hands taken after treatment when the patient was five years old showed the bones to be thick, short and dense. There was no evidence of rickets. The patient's skull has always been too long. This dolichocephaly is a result of synostosis of the sagittal suture which occurs in about 20 per cent of patients with vitamin D resistant rickets. Only the sagittal suture becomes synostotic and a compensatory overgrowth of the other sutures accounts for the increased length of the skull. A recent film, taken after treatment, showed no evidence of rickets. The cartilage was of normal width, and the zone of provisional calcification crossed the metaphyseal ends of the bones.

Dr. Lloyd H. Smith, Jr.[*2]: We have asked Dr. Gilbert Gordan to open the discussion on this very interesting problem in calcification. Dr. Gordan is Professor of Medicine at the University of California and has long been interested in problems of calcium and phosphorus metabolism.

Dr. Gilbert S. Gordan: In the case presented today, two features of particular importance are demonstrated. In spite of the patient's short stature, he really appears quite well, not at all like the classic picture that has been associated with severe rickets. Secondly, at present he shows no bone tenderness whatsoever—an important point to which I will return. Dr. Steinbach demonstrated that the patient did indeed have rickets. The disease developed despite a normal intake of vitamin D. Since large doses of vitamin D were required for improvement to be evident, the term *vitamin D-resistant rickets* seems appropriate. This term, however, is not a diagnosis because vitamin D-resistant rickets can occur when osteomalacia, that is, the softness of the bone, results from a primary defect in any one of three sites—the gut, the bone, or the kidney.

In adult medicine we are most likely to see osteomalacia in patients with intestinal malabsorption, particularly after gastrectomy or in the gluten-sensitive sprue syndrome. It can also occur in other diseases associated with steatorrhea. The bone as a site of resistance to vitamin D is exemplified by hypophosphatasia, a rather rare condition which need not be considered here since this patient's alkaline phosphatase level was repeatedly elevated. There are several kinds of renal defects that can produce this condition. One, in which there are tubular defects with loss of calcium or of phosphate or both, is characterized by the congenital tubular nephropathy of Debré, deToni and Fanconi. Patients with this syndrome have renal loss of phosphate and sometimes of calcium, amino acids and glucose—which the patient in the present case has not shown. A somewhat similar acquired syndrome can occur when the renal tubules are damaged by other conditions such as multiple myeloma or sarcoidosis. Another group of renal diseases which can cause osteomalacia are those associated with azotemia and acidosis.

The term *hypophosphatemic rickets* has always seemed vague to me, since hypophosphatemia can result from a congenital tubular anomaly such as the Fanconi syndrome or from a functional tubular phosphate leak due to secondary hyperparathyroidism. The latter homeostatic mechanism is invoked in response to the hypocalcemia of many types of osteomalacia.

In Major's *Classic Descriptions of Disease,* Dr. Thomas Cadwalader was credited with describing a case of osteomalacia. He said: "About the Beginning of Winter, of 1740, she had such a Weakness and Pain in her Limbs as to confine her to Bed altogether; and in a few Months afterwards the Bones in her Legs and Arms felt somewhat soft to the Touch, and were so pliable, as to be bent into a Curve; nay, for several Months before her Death, they were as limber as a Rag, and would bend any way with less Difficulty than the muscular Parts of a healthy Person's Leg, without the Interposition of the Bones." This patient died in 1742, and Cadwalader performed an autopsy, one pertinent portion of which is that upon making incisions in her legs and arms, "I found the outer Lamina of the Bones soft, and perfectly membranous, about the Thickness of the Periosteum." He said also that "She was, when in Health, five Foot high, as I was informed by her Husband; but having measured her after Death, she was no more than three Foot seven Inches in Length, tho' all her limbs were stretched out strait."[4] This may or may not be a case of osteomalacia. The x-ray films, laboratory data, and histologic sections do not seem to be available. Dr. Paul Fourman has made two rather interesting suggestions about Cadwalader's case: That it was really a case of hyperparathyroidism and, because the case was plagiarized by another Welshman, Dr. Bevan, who reported it in the Transactions of the Royal Society, that this was perhaps the sort of thing that led to the War of Independence.[10] In any event, this particular description is fitting for the classic type of very severe rickets that used to be seen.

[*1] Professor of Radiology.

[*2] Professor and Chairman, Department of Medicine.

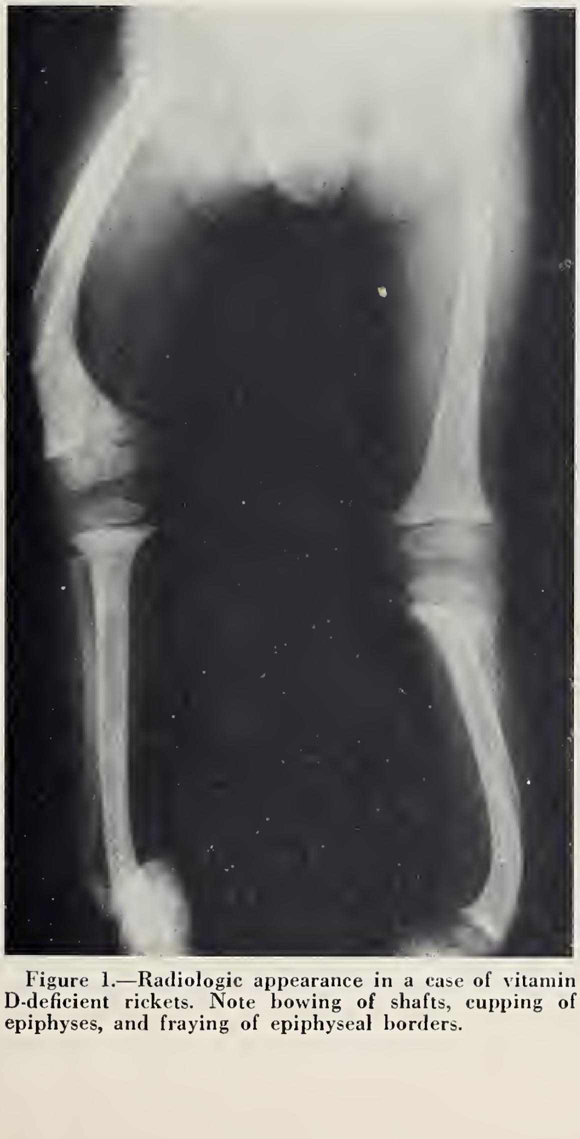


Figure 1.—Radiologic appearance in a case of vitamin D-deficient rickets. Note bowing of shafts, cupping of epiphyses, and fraying of epiphyseal borders.

Figure 1 shows the radiologic appearance of a youngster who was raised on mother's milk and jelly beans with resultant typical vitamin D-deficient rickets demonstrating the features that Dr. Steinbach discussed in the patient presented today. Vitamin D-deficiency is now a very rare disease in this country, although it is still found in less affluent places. I used to apologize for lecturing about rickets because it is so unusual a condition. However, it now appears that the adult form of osteomalacia is a very common condition if one looks through gastrointestinal clinics. Of course, the most common cause is any type of steatorrhea. We have studied a number of patients with osteo-

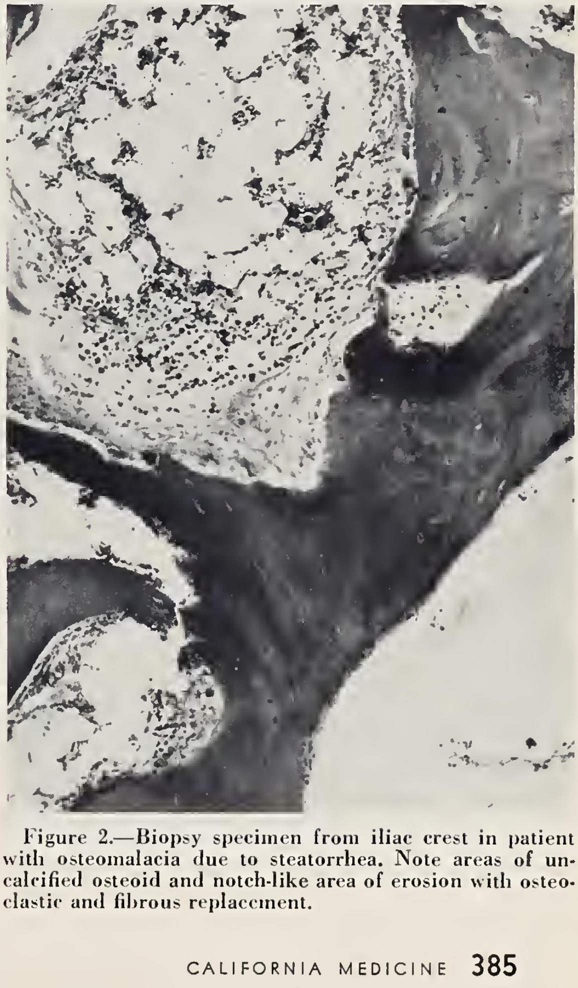


Figure 2.—Biopsy specimen from iliac crest in patient with osteomalacia due to steatorrhea. Note areas of uncalcified osteoid and notch-like area of erosion with osteoclastic and fibrous replacement.

malacia and in 1957 Dr. J. Picchi reported some of these.[18] This report could now be expanded considerably by the 52 cases collected subsequently. However, the moral of the story remains the same and, in the interest of historical accuracy, I would like to show that the important features have been known for some time.

Biopsy of specimens from the iliac crest, even with decalcified bone sections, shows the typical lesion which defines osteomalacia (Figure 2). This lesion is the osteoid seam, or an area of bone matrix in which calcification has not occurred. Osteomalacia means softness of the bones, and the softness is due to the lack of the minerals, calcium and phosphate, with the result that the osteoid tissue is not only poorly calcified but is actually exuberant. It is probably the compensatory overgrowth of the osteoid which distends the periosteum and causes the exquisite bone tenderness so characteristic of active osteomalacia.

In osteomalacia from any cause, the cortex is the part of the bone that is principally lost. The bone may be so soft that invagination of the acetabula occurs, forming a three-leaf shaped pelvis—"trifoliate pelvis"—(Figure 3). The pathognomonic roentgen lesions are bilateral symmetrical pseudo-fractures (Figure 4) usually called "milkman's syndrome" in this country, although described 10 years earlier by Looser[17] in Germany. Looser's contention that these "umbauzonen" are typical of osteomalacia was thoroughly confirmed by Albright and coworkers[1] in 1946 who observed a group of patients with milkman's syndrome all of whom had the histologic and chemical changes typical of osteomalacia. Pseudo-fractures probably result from the softness and compressibility of the bone. Steinbach, Kolb, and Gilfillen demonstrated that these pseudo-fractures represent grooves in the bone, occurring at sites where pulsating arteries overrun the soft bone, and are produced perhaps by the constant arterial pounding.[19] In less severe cases, radiologic evidence of involvement of the skeleton in osteomalacia can be minor, and in many cases the bones may appear normal by x-ray examination despite severe chemical osteomalacia.

Secondary hyperparathyroidism may be evident radiologically, especially in films of the hand. Figure 5 shows subperiosteal resorption typical of hyperparathyroidism in patients with intestinal malabsorption. These lesions disappeared after the patients' osteomalacia had been corrected. The reason for hyperparathyroidism in osteomalacia is currently under reconsideration. The role of the parathyroid glands is uncertain because difficulties exist in the measurement of parathyroid peptide

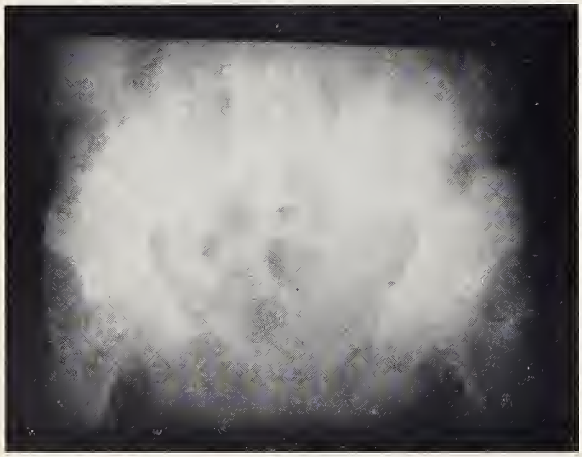


Figure 3.—Trifoliate pelvis resulting from invagination of acetabula into pelvic cavity in patient with osteomalacia due to steatorrhea.

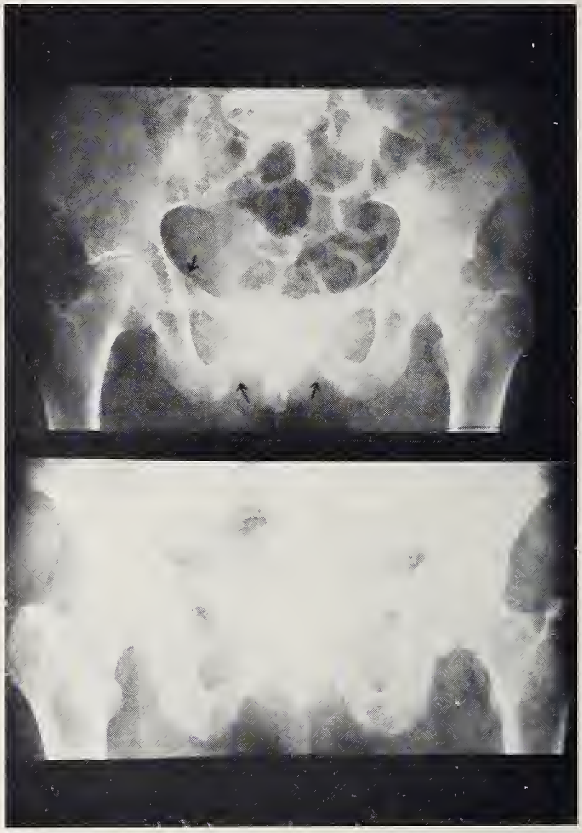


Figure 4.—*Upper Film:* Bilateral, symmetrical pseudofractures in 57-year-old woman with steatorrhea following gastroileostomy. *Lower Film:* Same patient after six months of treatment with vitamin D and calcium before surgical revision of gastroenterostomy.

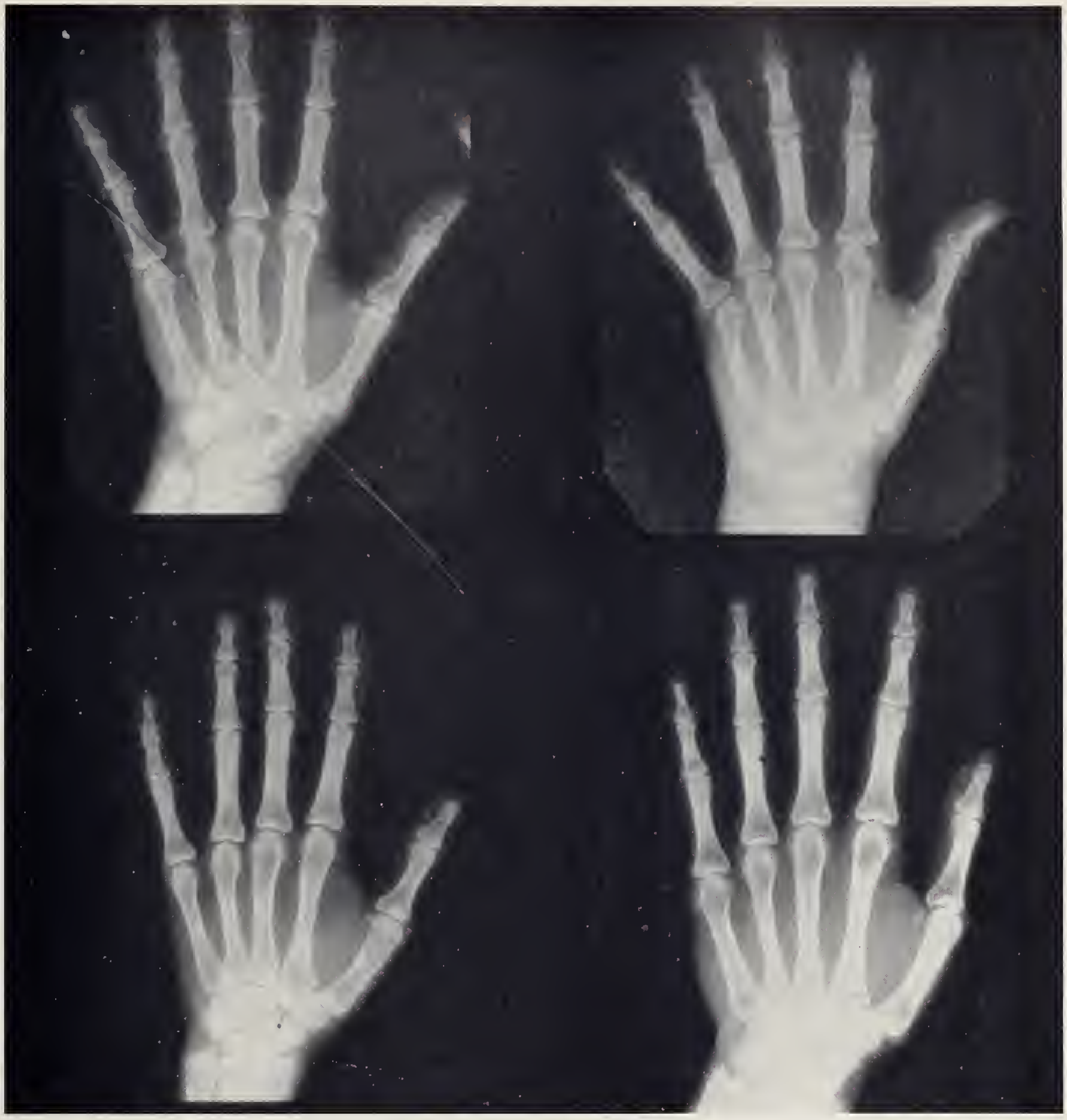


Figure 5.—Roentgenograms of hands of four patients with osteomalacia due to steatorrhea associated with four different intestinal diseases. Note subperiosteal resorption of radial surface of distal phalanx of index and middle fingers.

in blood. With the new techniques of Berson and Yalow, however, I think this will be solved.[3] It has been known for many years that in osteomalacia the parathyroid glands may be greatly enlarged, and Dr. J. Erdheim in 1907 pointed out that when he produced experimental osteomalacia in rats, parathyroid hyperplasia resulted.[8] In fact, the hyperplasia in some cases can go on to adenomatous hyperplasia. There are now four cases reported in which patients with longstanding sprue and osteomalacia were also found to have parathyroid adenomas.[6,13] Whether this combination is coincidental or represents "tertiary hyperparathyroidism" with autonomous overfunction resulting from very prolonged stimulation is not yet known. The answer may come from a similar situation where tertiary hyperparathyroidism appears to result from the secondary parathyroid hyperplasia of advanced renal insufficiency.[5]

Table 2 summarizes the studies in the patients collected by Picchi in 1957. These patients had bone pain and tenderness, bone deformities and elevated serum levels of alkaline phosphatase. Not all had hypophosphatemia; in fact, most of them had normal serum phosphate levels. These patients had far-advanced, longstanding osteomalacia due to intestinal malabsorption. A few had severe tetany but many of them did not, even with calcium levels of 7 or 8 mg per 100 ml, suggesting adaptation to hypocalcemia. Four of these five patients showed a tremendous calcium avidity. In this type of osteomalacia the patient usually can be shown to have a very great avidity for administered calcium. Calcium goes into the bone; none comes out in the urine. For the same reason, the endogenous urine calcium excretion is very low or nil. You will recall that the patient presented today had a urine calcium excretion of about 150 mg in 24 hours. This is a helpful point in determining the cause of this disease, suggesting a renal calcium leak rather than intestinal malabsorption. You will also notice in Table 2 that the patients reported by Picchi had a subnormal rise of the serum phosphate level in response to a calcium infusion. It normally rises 0.9 mg per 100 ml or more. The evidence that the underlying defect in bone mineralization is due to inadequate amounts of calcium and phosphate in the blood can be shown by a simple clinical technique, measuring the calcium X phosphate product. Obviously, we cannot measure a chemical solubility product directly by such crude techniques, but in these patients the product is almost always subnormal, instead of the normal 40.

The gastrointestinal lesion associated with osteomalacia in about half of the cases I have observed is malabsorption subsequent to operation for peptic ulcer, and in the other half it is gluten-sensitive steatorrhea. A few cases are due to regional enteritis, Whipple's disease, lymphoma, and occasionally carcinoma. However, patients with intestional malabsorption need not have the classic complaints of diarrhea, foamy, foul stools and emaciation. They may even be constipated and obese and the steatorrhea may be occult, requiring appropriate laboratory testing. In all cases except one, the tubular reabsorption of phosphate (TRP) has been distinctly abnormal. In most it was low, probably due to secondary hyperparathyroidism; in others, the tubular reabsorption of phosphate was very high. In some of these patients the value may be suspect, for if the serum phosphate level is extremely low, perhaps too little phosphate is filtered for any to appear in the urine. In many patients the serum phosphate level is quite normal. It has been postulated by others that such patients may have an exhaustion of the parathyroid glands. The proof of this must await direct measurements of the parathyroid peptide in the serum.

The more typical situation in patients with malabsorption is frank secondary hyperparathyroidism which can be demonstrated by bone biopsy, X-ray studies and a low TRP. Although the TRP is low, not all of these patients have hypophosphatemia. In fact, in our adult cases, normophosphatemia is more common than hypophosphatemia. The low TRP, or tubular renal phosphate leak, is so common in osteomalacia that Dent postulated in 1952 that renal tubular rickets was the most common single form of osteomalacia.[7] This conclusion seemed strange, since similarly low TRP's are found in patients in whom the osteomalacia is clearly due to intestinal malabsorption. Furthermore, Picchi in our group showed in 1957 that the renal phosphate leak, measured by the low per cent tubular reabsorption of phosphate, can be turned off by

TABLE 2.—*Osteomalacia due to Intestinal Malabsorption. Summarization of Studies of Patients Collected by Picchi in 1957*

Case No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Sex	F	F	F	F	F	F	F	F	F	M
Age	78	55	48	56	54	52	40	26	33	72
Bone Pain	+	+	+	+	+	+	+	0	+	+
Pathological Fractures	+	+	0	+	+	+	+	0	+	+
Alk. Phosphatase (Bodansky units)	18	15	19	12	14	10	26	13	5	20
Serum PO_4 (mg/100 ml)	3.6	3.6	3.2	2.3	4.2	3.4	2.5	0.7	3.6	2.3
Serum Ca (mg/100 ml)	7.1	8.8	8.0	6.8	8.8	8.6	9.1	5.1	6.5	8.2
Ca × P (normal >40)	26	32	26	16	37	28	23	4	23	19
Per cent TRP (normal 80-90)	46	66	70	69	92	96	93	100	92	90
Ca infusion:										
Per cent retained (normal 35-65)	96	90	73	91	100	72	62	82	75	72
Rise of serum PO_4 (normal >0.9) (mg/100 ml)	0.7	0.4	0.7	0.5	0.5	0.7	0.6	1.3	1.3	0.7

Ca=calcium; P=phosphorus; PO_4=phosphate; TRP=tubular reabsorption of phosphate.

infusion of calcium in malabsorption osteomalacia. This work was quickly confirmed by others, including Fraser of Toronto,[11] Fraser of London,[12] and Field and Reiss of St. Louis.[9] The phosphate leak in these cases, then, is clearly not causative; it probably represents the response of the parathyroid glands to hypocalcemia.

How does steatorrhea cause osteomalacia? In the past it was thought that calcium was bound to fat in the gut, forming calcium soaps which prevented normal absorption of calcium. Albright disproved this by demonstrating that patients with steatorrhea could absorb calcium after intramuscular administration of vitamin D. It then was suggested that the steatorrhea washed out the fat-soluble vitamin D. This seemed reasonable until the quantitative aspects were studied. For example, most patients with steatorrhea lose less than 40 per cent of their dietary fat in the stool. Steatorrhea, therefore, might waste a third or even a half of dietary fat-soluble vitamin D. But osteomalacia cannot be cured by simply doubling or tripling the normal vitamin D intake. Usually, fairly large doses—100,000 or even 1,000,000 units a day—are required. In addition, it has now been shown that the vitamin D absorption of patients with steatorrhea is only moderately reduced. A recent report demonstrates that normal subjects absorb approximately 60 to 90 per cent of an administered dose of tritiated vitamin D. Patients with steatorrhea absorb from zero to 50 per cent.[20]

Clearly, the discrepancy in most cases is not quantitatively enough to explain the clinical phenomenon. Perhaps the best explanation is one recently reported by Avioli on 28 January 1966, in New Orleans.[2] He found that normal subjects have in their blood large amounts of vitamin D and two metabolites of vitamin D. One of these metabolites is highly polar, contains two double bonds, and is active as shown by the line test (the standard U.S.P. test for vitamin D); the other metabolite is inactive. Avioli was able to show that in a group of patients with "hypophosphatemic osteomalacia" from North Carolina, the blood content of these two metabolites of vitamin D was extremely low and that of the active metabolite was nearly nil. Therefore, it seems possible that the defect may be inability to form the active metabolite of vitamin D.

Returning to the patient presented today, I think we can say that he probably does not have the intestinal type of lesion. He has calcium in his urine, and his serum carotene and cholesterol levels are both normal, which would be unusual in malabsorption. He still has a very low TRP, and it was not raised to normal by prolonged treatment with vitamin D. He is unable to conserve phosphate, as shown by the fact that on a low-phosphate diet his TRP remained 70 per cent instead of the 90 per cent that normal persons can achieve. He also has aminoaciduria. This latter point does not rule out an intestinal cause of osteomalacia. In a very beautiful study, Jonxis[15] from Groningen in the Netherlands showed that in rickets aminoaciduria also occurs, but that it disappears when the patient's disease is corrected by the administration of vitamin D. He has also showed that the aminoaciduria in these patients has a quite different pattern than in the Fanconi syndrome, where a generalized aminoaciduria is present. The amino acids present in the urine of patients with rickets not caused by a primary renal tubular defect are glycine, lysine, alanine, threonine, histidine, and serine. Since the aminoaciduria has persisted in the patient we are discussing today, despite vitamin D therapy, it would be worthwhile to determine the pattern of amino acids in the urine. I would predict now from the information we have accumulated in the last few days that this pattern will be one of pan-aminoaciduria.

The treatment has not been discussed. Obviously, if the underlying disease is gluten-sensitivity, gluten should be removed from the diet. If the patient has a gastroileostomy, revision of this to a gastrojejunostomy may be curative. If the patient has renal acidosis, treatment with alkali is indicated. In most cases, vitamin D resistant rickets is cured by large doses of vitamin D, and, as Dr. Francis Scott Smyth tried to teach me when I was a very young medical student, this agent may be hazardous. At first, large doses of vitamin D must be given to obtain good bone calcification and a normal serum calcium. The time comes, however, when the skeletal sponge becomes saturated and the calcium no longer is absorbed by the bones. Instead, it rises in the blood. It is very important to observe the serum calcium level closely and frequently in these patients to avoid vitamin D toxicity. The urine calcium excretion, either quantitatively or as determined by the Sulkowitch test, may be misleading since large doses of vitamin D lower the tubular resorption of calcium, allowing hypercalciuria despite a low serum calcium level.[14,16]

In this particular patient, there may be another method of treatment. I would like to return to the previously mentioned Cadwalader for a suggestion about the treatment of patients with this type of osteomalacia. At the end of Cadwalader's discussion about his case he noted:

> "Quaere, Whether a corrosive, acid State of the Fluids, might not have been the Cause of this uncommon Dissolution of the Bones? Supposing, therefore, a corrosive, acid State of the Fluids, to have been the proximate Cause; Quaere, Whether an alcaline Regimen, timely pursued, would not have been the most likely Method to have succeeded in this poor Woman's Case?

DR. L. H. SMITH, JR.: This is a tremendous calcium sweep—from the 16th century to today. Dr. Eisenberg.

DR. EUGENE EISENBERG*[3]: I would like to return to today's patient for just a moment. I have a very short story to tell about him. A 24-hour urine collection arrived in my laboratory last week without warning. It was marked, "Please check for hypophosphatasia." I overcame my initial impulse to pour it down the drain and called the housestaff to find out what they really had in mind. It turned out to be from a patient with medullary sponge kidney with low normal alkaline phosphatase. Sharing that patient's room in the Clinical Research Center was today's patient, and I asked about him. I heard the story that you heard given by Dr. Love today. There were a few additional features which struck my attention. One was that in spite of the patient's obvious rickets, the serum alkaline phosphatase was never greatly elevated for a child his age. A second point was that at the patient's young age he had already lost several incisor teeth and I believe one cuspid tooth. I wondered if this patient had hypophosphatasia, and I asked the housestaff to collect a spot urine specimen for me. On an aminoacid analysis run this morning we saw that the patient did have generalized aminoaciduria. However, in addition, he has a significant amount of phospho-ethanolamine in the urine. This is found only with hypophosphatasia.

---

*[3]Associate Professor of Medicine.

REFERENCES

1. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., and Roos, A.: Osteomalacia and late rickets, Medicine, 25:399, 1946.
2. Avioli, L. V., McDonald, J. E., Williams, T. F., and DeLuca, H.: The metabolism of tritiated vitamin D_3 in vitamin D-resistant rickets and familial hypophosphatemia, Clin. Res., 14:97, January 1966 (Abstract).
3. Berson, S. A., Yalow, R. S., Aurbach, G. D., and Potts, J. T., Jr.: Immunoassay of bovine and human parathyroid hormone, Proc. Nat Acad. Sci., 49:613, 1963.
4. Cadwalader, Thomas: Osteomalacia in Classic Descriptions of Disease (Major, R. H., Ed.), Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1932, pp. 261-264.
5. Case Records of Massachusetts General Hospital, New Engl. J. Med., 264:943, 1963.
6. Davies, D. R., Dent, C. E., and Willcox, A.: Hyperparathyroidism and steatorrhea, Brit. Med. J., 2:113, 1956.
7. Dent, C. E.: Rickets and osteomalacia from renal tubule defects, J. Bone Joint Surg., 34-B:266, 1952.
8. Erdheim, J.: Uber epithelkorperbefunde bei osetomalacie, Sitzungsb. d. k., Akad. d. Wissensch. Math. Naturw. Cl., 116:311-370, June 1907.
9. Field, M. H., and Reiss, E.: Vitamin D-resistant rickets: The effect of calcium infusion on phosphate reabsorption, J. Clin. Invest., 39:1807, 1960.
10. Fourman, Paul: Parathyroids and Tubular Function in Hormones and the Kidney (Williams, P. C., Ed.), Academic Press, London and New York, pp. 133-138.
11. Fraser, D., Leeming, J. M., Cerwenka, E. A., and Kenyeres, K.: Studies of pathogenesis of high renal clearance of phosphate in hypophosphatemic vitamin D-refractory rickets of simple type, Amer. J. Dis. Child., 98:586, November 1959 (Abstract).
12. Fraser, R., and Nordin, B. E. C.: Phosphate-losing osteomalacia and its parodoxical relief by large doses of vitamin D, J. Clin. Endocr., 14:785, July 1954 (Abstract).
13. Gordan, G. S., Eisenberg, E., Loken, H. F., Gardner, B., Hayashida, T.: Clinical endocrinology of parathyroid hormone excess, Recent Progr. Hormone Res., 18:297-336, 1962.
14. Gordan, G. S., Loken, H. F., Blum, A., and Teal, J. S.: Renal handling of calcium in parathyroid disorders, Metabolism, 11:94-102, January 1962.
15. Jonxis, J. H. P.: Some investigations on rickets, J. Pediat., 59:607, 1961.
16. Litvak, J., Moldawer, M. P., Forbes, A. P., and Henneman, P. H.: Hypocalcemic hypercalciuria during vitamin D and and dihydrotachysterol therapy of hypoparathyroidism, J. Clin. Endocr., 18:746, 1958.
17. Looser, E.: Uber pathologische formen von infraktionen und callusbildungen bei rachitis und osteomalacie und anderen knochenkrankungen, Zentralblatt fur Chirurgie. 47:1470, 1920.
18. Picchi, J., Crane, J., Gordan, G. S., Sakai, H. Q., and Steinbach, H.: Parathyroid function in malabsorption osteomalacia, Clin. Res. Proc., 5:67-68, January 1957 (Abstract).
19. Steinbach, H. L., Kolb, F. O., and Gilfillen, R.: Mechanism of production of pesudofractures in osteomalacia (Milkman's syndrome), Radiology, 62:388, 1954.
20. Thompson, G. R., Lewis, B., and Booth, C. C.: Absorption of vitamin D_3-^3H in control subjects and patients with intestinal malabsorption, J. Clin. Invest., 45:94, 1966.

Editor
DWIGHT L. WILBUR, M.D.
•
Acting Editor
EDGAR WAYBURN, M.D.
•
Assistant to the Editor
ROBERT F. EDWARDS
For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MacLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

California Medicine

EDITORIAL

An Outside Look At Medical Education

Twice in the 20th century the American Medical Association has requested an external examination of the state of medical education and has sought recommendations for changes to ensure continuing excellence. In 1910 the famed Flexner report was wholeheartedly implemented by the AMA. The report and the implementation had a profound effect on the development of American medical education and among other effects assured the benign dominance of the AMA in this field.

In 1966 another external examination, commissioned by the Board of Trustees has been published. Known by the name of its chairman, John S. Millis, president of Western Reserve University, the Report of the Citizens Commission on Graduate Medical Education has analyzed and criticized the state of medical education in America today.

This is no Flexner report with detailed and scientific factual analysis. Rather it is an overlook which raises and identifies the issues as the commission sees them.

The report points out:

- The complexity, the fragmentation and the inflexibility of standards for graduate medical education.
- The discontinuity of the educational process, divided as it is into its separate parts—the premedical period, the medical school, the internship, and the residency.
- The persistence of the idea of apprenticeship in the process of education and training.
- The ineffectiveness and the inadequacy in the organization of many of our present institutions.
- The unsatisfactory balance between generalization and specialization.
- The deep concern of the public in all matters concerning medicine.

The report offers a number of recommendations. Probably none of us will agree with all of them. But in criticizing them individually it is highly important to view them in the context of the report as a whole, and to bear in mind that this is a first step by the AMA to bring into focus our current problems in graduate education.

We believe that the AMA and physicians throughout the country are capable of accepting the responsibility of guiding the medical profession in the decisions which must be made. Every physician should familiarize himself with the contents of the Millis report, in particular, since it is the product of a citizen's commission appointed by the AMA and will be under discussion in the AMA Board of Trustees and the AMA House of Delegates. Every component medical society should review this study so that the decisions finally arrived at will reflect the wills, desires and expectations of physicians in the future development and directions of medical education.

Only in this way will we ensure professional control of the direction of medical education. To do less would be to abdicate a primary responsibility the medical profession has to itself and to the public. In the words of the chairman of the Citizens Commission: "For any learned profession there are but two alternatives for establishing standards of practice and education. Responsibility can be assured by Society as a whole, operating through government, or it can be assumed by the organized profession through a voluntarily accepted self-discipline."

California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 524th Meeting of the Council, San Diego, Hotel Del Coronado, 17 to 18 September 1966.

The meeting was called to order by Chairman Anderson at the Hotel Del Coronado, San Diego, on Saturday, 17 September 1966, at 8:35 a.m.

Roll Call

Present were President MacLaggan, Speaker Quinn and Councilors Isenhour, Eastman, Melone, Todd, Gooel, Taw, O'Connor, Ham, Rogers, Crum, Boyle, Maguire, Burnett, Richard S. Wilbur, Miller, Watts, Fenlon, Kay, Kaiser, Anderson, Yant, Grunigen, and Immediate Past President Teall. Absent for cause were President-Elect Morrison, Vice-Speaker Telford, Editor Dwight L. Wilbur, Secretary Weyrauch and Councilors Bullock and Longmire.

A quorum present and acting.

Present by invitation were Messrs. J. Collins, Eberlein, Whelan, Thomas, Blackley, Bowman, Edwards, Clark, Klutch, E. Collins, Lemos, Hetland, Curley, Doctor Miller, Mmes. Griffith and Redfern, and Mlles. Price and Belser of CMA staff; Messrs. Hassard and Huber, legal counsel; component society executives Scheuber of Alameda-Contra Costa, Rideout of Butte-Glenn, Geisert of Kern, Sower of Marin, Colvin of Monterey, Somerville of Napa, Bannister of Orange, Walters of Riverside, Dochterman of Sacramento, Donmyer of San Bernardino, Nute of San Diego, Neick of San Francisco, Wood of San Mateo, Marvin of Santa Barbara, Brown of Sonoma, Whitehall of Stanislaus, and Bruce of Tulare; Messrs. Paton, Babb, Heller, Light and Potloff of California Physicians' Service; Messrs. Read and Brown of the Public Health League; Doctor Nelson of Stanford School of Medicine; Doctor Bostick of UC, California College of Medicine; Mr. Ward of the State Health and Welfare Agency; Doctors Breslow and Day of the State Department of Public Health; Doctor Lowry of the State Department of Mental Hygiene; Doctor Young of the State Department of Rehabilitation; Doctor Combs of the State Board of Medical Examiners; Mrs. Bacon of the Woman's Auxiliary to the CMA; Mrs. Stanley of the California Nurses' As-

JAMES C. MACLAGGAN, M.D.	President
JOHN G. MORRISON, M.D.	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH W. TELFORD, M.D.	Vice-Speaker
CARL E. ANDERSON, M.D.	Chairman of the Council
ALBERT G. MILLER, M.D.	Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D.	Secretary
DWIGHT L. WILBUR, M.D.	Editor
EDGAR WAYBURN, M.D.	Acting Editor
HOWARD HASSARD	Executive Director

General Office, 693 Sutter Street, San Francisco 94102 • 776-9400

ED CLANCY	Southern California Office

1515 N. Vermont Avenue, Los Angeles 90027 • 663-8071

sociation; Doctors Millar, Kilroy, Howard, Snyder, Salmon, Sherman and others.

1. *Minutes for Approval*

Minutes of the 523rd meeting of the Council, held 30 July 1966, were approved with two corrections:

(a) Item 23, Direct Billing Under Title 19, was revised to read: "Voted to direct the Chairman of the Council to appoint a committee to look into the problem of direct billing under Title 19, to attempt to clarify previous misinformation on the subject, and to report back to the Council with recommendations.

(b) Correct spelling of the name of the new Chairman of the Department of Internal Medicine at the University of California School of Medicine at Davis, which is as follows: Robert Bolt, M.D.

2. *Membership*

(a) Fifty-eight members whose dues were delinquent and now paid, were reinstated.

(b) Four applicants were voted election to Associate Membership. These were: William Martin Klemme, Marin County; Harold N. Mozar, Sacramento County; J. Peter Oswald, San Joaquin County; Marvin P. Eisenberg, Ventura County.

(c) Two members were voted election to Retired Membership. These were: Cuthbert M. Fleissner, Mendocino-Lake County; Frederick W. Kroll, San Francisco.

(d) A reduction of dues was voted for eleven members for reasons of prolonged illness or postgraduate education.

3. *Reports of the President and President-Elect*

President MacLaggan reported that CMA had cooperated with the California Highway Patrol in a Labor Day program that was broadcast throughout the state to try to cut down the number of traffic fatalities over the holiday weekend.

In the absence of Doctor Morrison, President MacLaggan also gave the report of the President-Elect. Doctor Morrison attended a subcommittee meeting of the "543" Committee where a decision was made to send CMA representation to a conference on the formation of a Health Manpower Council, to be held in Santa Barbara on 1 and 2 October. Many allied health organizations have been contacted and will be represented at the meeting. CMA will be represented by President-Elect Morrison and Councilor Melone.

4. *Finance Committee*

Chairman Kay reported that at a committee meeting held the night previous to the Council meeting, the reports of the auditors had been reviewed. He announced that each member of the Council would have a copy of the report by the next Council meeting, and that it also would be made available to any member of the CMA wishing to review it, in accordance with the 1966 House of Delegates Reference Committee recommendation. Doctor Kay expressed the thanks of the Finance Committee to Mr. Lytton Hetland for assistance in preparing the report.

5. *Acting Editor for* CALIFORNIA MEDICINE

Chairman Anderson announced that Doctor Dwight Wilbur requested Council approval for Doctor Edgar Wayburn to act as editor of CALIFORNIA MEDICINE for the two months' period during which Doctor Wilbur will be absent.

ACTION: Voted to approve Doctor Edgar Wayburn's appointment as acting editor of* California Medicine *during the two months' absence of Editor Dwight Wilbur.

6. *Bureau of Research and Planning*

Chairman Sherman reported that the Bureau has held two meetings since the reorganization of the Committee on The Role of Medicine in Society, the Committee on Organizational Review and Planning and the Bureau of Research and Planning into three separate entities. He reviewed activities of the Bureau that had been undertaken in the past two meetings.

ACTION: Voted to approve the report of the Bureau.

7. *Committee on the Role of Medicine in Society*

In the absence of Chairman Watts, Mr. Murray Klutch reported that the Committee was developing a series of statements regarding medical care and medical practice, quality of medical care, the organization of the medical profession, and other subjects. He stated that the Committee hoped to have the first of this series available by the next Council meeting.

8. *Committee on Organizational Review and Planning*

Chairman Teall reported that the committee had begun deliberations by examining the objectives, functions and purpose of the CMA and concerned itself with the short-range challenges facing medicine within and without the organization, focusing on the health care of the public as a whole. The Committee recommended that the Council each year establish its objectives for the Association for that year, and that these decisions be made known to all commissions and committees for their guidance. It also recommended the addition of an academician and a public health physician to the Committee. The Council took no immediate action on these recommendations.

Chairman Teall submitted a series of recommendations relative to House of Delegates resolutions for Council approval, with the following results:

ACTION: Voted not to implement at this time Resolution 40-66, which proposed a CMA Candidate Forum.

ACTION: Voted to refer the matter of voluntary accreditation of health insurance plans (Resolution 57-66) to the Commission on Medical Services for further study.

ACTION: Voted to support the AMA-ERF program for student loans and requested that the Commission on Communications publicize this support, urging voluntary contributions—in accordance with Resolution 100-66.

ACTION: Voted to support Resolution 101-66 (reaffirming CMA's position on free choice of physician) being aware of the conflicting complications which it presents with the current Crippled Children Services program.

After some discussion of the role of the Committee on Organizational Review and Planning, the Council decided that the matter needed clarification.

ACTION: Voted to request the Committee on Organizational Review and Planning to delineate further its areas of responsibility and report back.

9. *Task Force on Public Law 89-97*

Chairman Teall discussed progress being made relative to the county/teaching hospital situation in California. He reported that a survey on the subject was initiated by the Bureau of Research and Planning in accord with Council directive and that, so far, responses had been received from 42 of the 104 teaching hospitals in the state. The responses are being referred to the subcommittee of the Task Force appointed to attempt to formulate a policy position for CMA on this complex subject. Doctor Teall stated that on the basis of survey results to date, there seemed to be no uniform pattern in the state regarding billing processes. The Task Force hopes to present recommendations on the problem at the next Council meeting.

10. *Organization of State Society Presidents*

Past-president Teall reported on the recent meeting of the Organization of State Medical Association Presidents, of which he served as president. One subject discussed at length was the attitude expressed by pharmaceutical firms that exhibits at annual medical society meetings and advertisements in medical journals are not achieving their desired objectives. This discussion prompted a recommendation requesting that AMA hold a national meeting of representatives of state associations and members of the Pharmaceutical Manufacturers Association. Mr. Murray Klutch, CMA staff member assisting Doctor Teall during his term as president of the national organization, was commended for his outstanding efforts.

11. *National Commission on Community Health Services*

It was announced that the final report of the National Commission on Community Health Services will be available in October. Chairman Anderson requested that each Councilor receive a copy of the report as soon as it is available.

12. *Annual Conference of Component Society Officers*

Councilor Eastman reported that at the initial planning meeting it was decided to utilize the same general format as was used last year. The morning session will concentrate on three major topics: Medicare and Medi-Cal, Medical Discipline, and Health Manpower and Medical Education. The afternoon will be devoted to smaller discussion groups. Doctor Eastman stated that although the program is still tentative, the meeting is definitely set for 14 January 1967, at the Airport Marina in Los Angeles.

13. *Ad Hoc Report on Workmen's Compensation*

Chairman Anderson reported that the new official minimum medical fee schedule of the Division of Industrial Accidents will follow the format of the 1964 *Relative Value Studies,* with a conversion factor of $5.50 to be effective 1 October 1966. He also reported that the roster of physicians desiring to do Workmen's Compensation practice is nearly ready to be published and probably will be available in November. Doctor Anderson announced that the Official Minimum Medical Fee Schedule is presently being printed by the CMA's 693 Sutter Publications Inc., and one copy will be sent to each member in the state free of charge. Additional copies will cost $1.00 each.

Due to the need for advice from the medical profession by the Division of Industrial Accidents on the matter of fees, Doctor Anderson moved that the Council recommend to the Committee on Committees that there be developed a small Council committee which would also act as a sub-committee of the CMA Committee on Fees, to act as liaison to the Division of Industrial Accidents.

ACTION: Voted to authorize the Committee on Committees to appoint such a committee to act as liaison between the Council and the Division of Industrial Accidents.

Since the main work of the ad hoc Committee on Workmen's Compensation had been completed, Chairman Anderson expressed his feeling that although the committee should go out of existence, it was imperative that the excellent relationship that had been established with industry be maintained through the Industry Medical Committee. He recommended that the officers of CMA plus the chairmen of the CMA Committee on Occupational Health and Rehabilitation and the newly formed liaison committee to the Division of Industrial Accidents be the representatives for CMA on the Industry Medical Committee and meet with the top officials of industry, business, and insurance, on a continuing basis. It was moved that this mechanism of liaison within the Industry Medical Committee be approved.

ACTION: Voted to maintain liaison with the Industry Medical Committee through the above representatives of the CMA.

Chairman Anderson reported that S.B. 1134, requesting reimbursement for Workmen's Compensation on a usual and customary basis, was presently in interim study. He stated that it did not seem practical at this time to call for interim hearings, and would be more reasonable to take up the issue at the beginning of the new session of the Legislature.

Speaking for the ad hoc Committee, Doctor Anderson requested that the Committee be disbanded at this time, its work being essentially completed.

ACTION: Voted to disband the ad hoc Committee on Workmen's Compensation, with thanks.

14. *Commission on Medical Services*

Chairman Arthur Howard discussed the announcement that the schedule of maximum allowances for physicians' services under the new Dependents Medical Care contract was not to be published. General Peatfield of the Dependents Medical Care Administration stated that he would accept a new, higher schedule if it were not published. The opinion of the Commission was to inform physicians that they should bill their usual and customary fee, rather than inform them of the coefficient factor, and a recommended statement was presented as follows:

"1 July 1966, a new one-year contract became effective for the dependents of military personnel medical care program. Under the contract, physicians should bill their usual charges for services rendered using the 1964 *Relative Value Studies* nomenclature and code numbers. Payment will be made by the fiscal intermediary up to the maximum allowances in accordance with the contract."

ACTION: Voted to send a letter embodying the concepts in the above recommendation, augmented by further clarifying statements informing physicians that under the new one-year contract, billing on the basis of usual fees would not necessarily mean payment of that amount if it exceeded the unpublished ceiling in the schedule of maximum allowances.

Chairman Howard also reported that the Committee on Mediation had met and requested that the Council expand the Committee's activities to include cases referred by: "(1) Component society review committees; (2) insurance carriers for commercial programs only—no cases involving government programs would be reviewed; (3) non-member physicians, including expelled or rejected component society members; and (4) physicians or insurance carriers on cases which component society mediation committees decline or refuse to act."

ACTION: Voted to approve the above expanded activities.

15. *Committee on Legislation*

Chairman Kilroy reported to the Council that a letter had been received from Doctor William

Wickett, Jr., who is affiliated with the student health center at Fullerton State College. The letter pointed out the possible inadvertent violation by physicians of "ethics of confidence" in transferral of confidential information to non-medical persons with regard to health examinations required for teachers applying for positions within the Public School System in California. It was the recommendation of the Legislative Committee to draft a corrective proposal which would come back to the Council for review before being introduced.

ACTION: Voted to authorize the Committee on Legislation, in consultation with other informed individuals, to draft a proposed bill to carry out the intent of the correspondence from Doctor Wickett.

At Doctor Kilroy's request, Mr. Ben Read discussed some problems facing the Committee, particularly those relating to the subject of therapeutic abortion.

The Committee on Legislation recommended that a letter be sent to legislators, administrative assistants and others involved in the introduction of legislation—after the election, but prior to 1 January. The letter would state that CMA and the Public Health League will be happy to consult with them on proposed medical legislation prior to its actual introduction into the Legislature.

ACTION: Voted to approve the intent of the Committee in offering help to those involved in introducing medical legislation.

The Committee presented recommendations on six House of Delegates resolutions—for Council approval:

CMA Resolution 15-66: Marijuana reclassification to a "dangerous drug." Recommendation—No.

CMA Resolution 29-66: Jurisdiction of pathologists regarding medical-legal investigation of deaths. Recommendation—Yes.

CMA Resolution 30-66: Extension of McAteer Bill regarding alcoholism for three years after 1 March 1967. Recommendation—Yes.

CMA Resolution 47-66: Hospital Board Members regarding a physician as a Board Member. Recommendation: Yes.

CMA Resolution 66-66: Continuation of Study Committees for Infant and Maternal Health. Recommendation: Yes.

CMA Resolution 84-66: Medical Library exemption from taxation. Recommendation—Yes.

ACTION: Voted to accept the recommendations as stated by the Committee on Legislation.

Mr. Read reviewed interim committee hearings on a variety of subjects, and reported that the Cal-Med proposal had been referred to the Interim Committee on Public Health for study.

Chairman Kilroy announced that the Committee on Legislation was sponsoring two regional meetings in September to give county legislative chairmen, medical executives, and others an opportunity to review candidates for the coming election. He also stated that late in September, the Public Health League will meet with representatives of the allied health professions to review candidates and determine which ones will receive endorsements.

16. *Commission on Community Health Services*

Chairman Kay announced that on 15 October, the Committee on Rural Health, Commission on Community Health Services, representatives of the deans of medical schools and student representatives of the medical schools, will meet at the Airport Marina in Los Angeles for a one-day conference to discuss the subject of young doctors going into rural health practice. The purpose of the meeting is to get the ideas of the students, and determine how CMA may be of assistance in making it more interesting and challenging for doctors to go into the field of rural health.

Chairman Kay introduced Doctor Leopold Snyder, chairman of the Committee on Rural Health. Doctor Snyder discussed the subject of clinics for migratory agricultural workers. A report was read, reviewing previous meetings on the matter of rendering adequate medical service to migrant farm workers during peak harvest seasons. It was pointed out that the Migrant Health Service wishes to contract directly with county medical societies to set up clinics, although they may contract with any non-profit agency, such as a county hospital, to establish this program. The clinics would be financed for the remainder of this year by an Office of Economic Opportunity grant.

ACTION: Voted to authorize the Committee on Rural Health to continue in its work with county medical societies in the implementation of the program and urged the Committee to continue its cooperation with the State in developing a health program for migrant workers.

The fluoridation education project, approved in principle by the Council at its previous meeting, was discussed. The administering organization for the project will be the Institute for Research in Childhood, Health and Education.

ACTION: Voted to approve continued action and exploration and to proceed with the presentation of the project proposal to the United States Public Health Service for a grant to undertake a joint fluoridation professional education project with the California Dental Association and the Southern California State Dental Association.

17. *Committee on Health Care of the Aging*

Doctor Pierre Salmon discussed the subject of reimbursement of physicians for time spent on utilization review functions for extended care facilities. He presented the following statement for Council consideration: "Because of the increasing demands on physician's time for administrative review functions, the CMA Committee on Health Care of the Aging recommends that a reasonable compensation may be received by physicians serving on extended care facility utilization review committees."

ACTION: Voted to oppose adoption of the recommended statement on compensation of physicians providing utilization review for extended care facilities.

18. *Commission on Hospital Affairs*

In the absence of Chairman Halter, Mr. William Whelan reported that the hospital medical staff survey program was continuing—at an accelerated pace. He said that some 50 of the 60 physicians appointed by the Council have participated in one or more surveys. He also announced that the State Department of Public Health and the Social Security Administration still had under advisement extension of a contract with the CMA to make some surveys in connection with the certification of hospital facilities under Medicare, Title 18.

19. *Reports of Medical Schools*

Doctor Bernard Nelson, representing Dean Glaser, reported that the Stanford School of Medicine had admitted 65 freshmen students out of 800 applicants and in addition, was admitting some students to second, third, fourth and fifth year programs. Doctor Nelson also announced that the Stanford Committee on Curriculum had been reorganized, and in the process a new Committee on Medical Education had been created to help physicians in postgraduate education. Some discussion was given to admission requirements and selection of students.

Doctor Warren Bostick of UC, California College of Medicine, reported that the new class of incoming freshmen had been lowered to a total of 64 students, as requested by the CCM governing board.

20. *State Health and Welfare Agency*

Administrator Paul Ward announced that final discussions on nursing home rates (retroactive to 1 July 1966) were then in progress. He also reviewed unavoidable differences between Titles 18 and 19 of Public Law 89-97 with regard to nursing homes.

Possible Congressional action to limit the dollar amount that can be granted to each state for Title 19 beneficiaries was also discussed.

Mr. Ward stated that the Health Review and Program Council established under A.B. 5 was ready to tackle the job of doing a cost breakdown on the program, in compliance with the Legislature's request.

21. *State Department of Public Health*

Director Lester Breslow reviewed recent activities of the Department and announced that its staff is enlarging. Two new staff members are Doctor Omer W. Wheeler, who is joining the Los Angeles office, and Doctor Crawford Bost, who will assist Doctor T. Eric Reynolds as Assistant Chief of the Division of Patient Care Facilities and Services.

Doctor Breslow also announced the meeting of the American Public Health Association, which will be held the last part of October and early November, in San Francisco. He invited the Council to attend if possible, and said that the program would be a very worthwhile one which could be attended on a one-day basis as well as for the week-long session.

22. *California Physicians' Service*

Board Chairman Richard Wilbur announced that Mr. Clinton Fair, Director of Social Insurance for the AFL-CIO, is a new member of the CPS Board, replacing Mr. Paul Schrade. Doctor Wilbur also reviewed the current situation regarding the processing of Medi-Cal and Medicare claims, stating that in accordance with directives from the Social Security Administration, CPS is taking steps to "streamline" the processes. Medical advisors, for example, are being given increased responsibility for determining "usual and customary" fees. In addition, CPS is encouraging more medical society review committees to establish and inform CPS of local "guidelines" for determination of fees, so that claims handling may be expedited.

23. *Medical Executives Conference*

In the absence of MEC Chairman Reuben Dalbec, Chairman Anderson announced that Mrs. Peggy Brock, Executive Secretary of Imperial County Medical Society, had been recommended for membership in the Medical Executives Conference.

ACTION: Voted to accept Mrs. Brock into membership in the Medical Executives Conference.

24. *State Board of Medical Examiners*

Doctor Robert Combs discussed the problem that under P.L. 89-239, some paramedical personnel are to perform functions for which they are not licensed by the Board of Medical Examiners or any other board. Councilor Taw drew Council attention to a problem presented to him by the CMA Anesthesiology Section regarding physicians' billing for services performed by nurses hired by anesthesiologists.

Doctor Taw said that the physician is billing for services he did not perform, whether he bills on behalf of the nurse, or bills directly and pays the nurse a salary. This has presented a disciplinary problem for the Anesthesiology Section, which requested that the Council reconsider the statement on "Compensation for Physicians' Services" adopted at the 7 May 1966 meeting of the Council.

ACTION: Voted to send a letter to the Anesthesiology Section, requesting them to submit a specific recommendation for action by the Council, as well as a similar letter to the Society of Anesthesiologists.

Discussion followed on the subject of licensing or recognizing various classifications of medical and surgical technicians.

ACTION: Voted to refer the question of classification of medical and surgical technicians to the Commission on Allied Health Professions and Services for further study and report back.

25. *California Nurses' Association*

Mrs. Mary Stanley, president of the Association, reviewed the recent crisis, and expressed her appreciation for individual physician support the Association had received during this difficult time. Mrs. Stanley also reported that the CNA Board of Directors had made a statement altering their policy so as not to preclude the possibility of striking, providing all other avenues had been pursued to their limits and had failed. Mrs. Stanley said that the Board felt that this policy would give nurses the techniques available to other employee organizations engaging in collective bargaining.

26. *Meeting with AMA Delegates*

Chairman Anderson announced that the CMA Delegation to the AMA will meet with the Council on the evening of Friday, 28 October, prior to the regular Council Meeting scheduled for 29 October.

27. *Ad Hoc Committee on Direct Billing Under Title 19*

On behalf of the ad hoc committee, Councilor Burnett read the report submitted for Council approval. As amended by the Council, the following recommendations were considered:

1. A factual report be made to the CMA membership documenting the history of the development of regulations under the Medi-Cal Law including a documentation of those gains which have been made in the use of a carrier as a fiscal intermediary and the inclusion of the concept of usual and customary fees, but also including a full documentation of the development of regulations relating to direct patient billing.

2. For Group II recipients, CMA press as strongly as possible for a recipient program now, as this seems to be that area of the law in which this could now be most readily implemented.

3. The CMA Council be requested to affirm its support of direct patient billing in all categories.

4. This latter recommendation be dependent upon the ad hoc committee on direct billing or that another committee be charged with the responsibility for developing a structure for ethical and responsible direct patient billing for CMA members, including a mechanism for the protection of the welfare recipient.

5. When such a structure has been developed, an appropriate representation be made to the appropriate state agencies to obtain an appropriate interpretation from HEW favorable to direct patient billing under current federal welfare laws.

6. The members be urged to make no challenge of the State law at this time.

ACTION: Voted to approve the report as stated above.

28. *Commission on Public Agencies*

Chairman Miller presented the following statements to the Council for its approval:

"The Committee on Mental Health agrees that Medi-Cal Regulations should be revised to provide *30* rather than 21 days inpatient psychiatric care without prior authorization and *nine* rather than five psychiatric outpatient visits within the six-month period following the first visit for psychiatric care without prior authorization."

ACTION: Voted to approve the extension of the psychiatric benefits under the Medi-Cal program.

"The Committee on Public Health urges that CMA support the Department of Public Health recommendation that Rubella be placed on the list of Notifiable Diseases in California."

ACTION: Voted to approve the recommendation of the Committee on Public Health.

The subject of the definition of Disorders Characterized by Lapses of Consciousness (as contained in the California Administrative Code, Title 17, Chapter 4, Subchapter 1—Reportable Disease and Conditions) received considerable discussion by the Council. It was included in both the report of the Committee on Traffic Safety and the Committee on Public Health. Doctor Miller offered a proposed definition to the Council on behalf of the Committee on Public Health. Following discussion, the middle paragraph of the original recommendation was restated as follows:

"Any person aged 14 years or older who, during the preceding three years, has experienced lapses of consciousness or episodes of marked confusion which may become chronic, shall be considered to have a disorder characterized by lapses of consciousness and shall be reportable."

ACTION: Voted to approve the recommendation of the Committee on Public Health as amended.

Chairman Miller recommended that the Council reaffirm its policy that mail ballots on appropriate subjects and under appropriate circumstances be acceptable for commission and committee decisions.

ACTION: Voted to reaffirm the Council policy on mail ballots.

29. *Commission on Allied Health Professions and Services*

Chairman Grunigen submitted to the Council for its approval a statement on the "Role of the Registered Nurse in Glaucoma Screening Tests." The first paragraph of the statement was amended to read:

"The California Medical Association and the California Nurses' Association acknowledge their acceptance of the propriety of a registered nurse to perform certain functions *in the process of glaucoma screening tests."*

ACTION: Voted to approve the statement as amended in italicized portion above.

A proposed statement by the California League for Nursing on inhalation therapy and the importance of nurses being familiar with such techniques, was offered by the Commission for Council approval.

ACTION: Voted to approve the statement on inhalation therapy.

Chairman Grunigen offered a joint statement of the California Medical Association and the California Nurses' Association on Tuberculin Skin Testing for the consideration of the Council. The statement supported the concept that a registered nurse could administer, observe, measure, and record tuberculin tests, under the conditions set forth in the statement.

ACTION: Voted to approve the joint statement as presented by the Commission.

30. *Medicine and Religion*

Doctor Grunigen expressed the request of the Committee on Medicine and Religion for permission to hold a conference during the 1967 Annual Session. The title of the conference was discussed and was changed to "Medical and Moral Aspects of the Use of New Procedures in Medicine."

ACTION: Voted to grant permission to the Committee to hold the above conference.

Doctor Grunigen also requested Council approval for the Committee on Medicine and Religion to cooperate with the UCLA Extension Service in a Symposium on Medicine and Religion to be held in November 1966.

ACTION: Voted to approve the cooperative efforts of the Committee on Medicine and Religion with the UCLA Extension Service in holding the symposium.

31. *Staff Report*

Mr. Howard Hassard reported that in accordance with the bylaw amendment adopted by the last House of Delegates regarding "provisional membership" in the CMA, it was incumbent on the Council to set a dues level for this category. He said that it was the recommendation of the staff that the dues level be set at not more than $20 per year.

ACTION: Voted to establish a dues amount of $20 per year for "provisional membership" in CMA.

32. *Advertising by Clinical Laboratories*

After some discussion of the possibility of advertisements by clinical laboratories being accepted for publication in CALIFORNIA MEDICINE, the Council decided that the matter needs further study.

ACTION: Voted that it be the policy of* California Medicine *not to accept advertisements from clinical laboratories at this time.

33. *Direct Billing by Automated Laboratories*

The Council considered a resolution submitted by Doctor George Herzog, Jr., on behalf of the San Francisco Medical Society. The resolution stated that: (1) Savings incurred by the employment of automated laboratories should be passed directly to patients through direct billing to patients by the laboratories; (2) recognition of the value of professional services (drawing of blood, packaging and sending specimens to the laboratory) should be compensable with a value of no more than one unit on the *RVS*; and (3) this principle be conveyed to the California Hospital Association so that such savings might be passed on to patients when hospitalized as they are when patients receive such services on an out-patient basis.

ACTION: Voted to refer the resolution to the Committee on Fees for study and recommendations.

34. *Laboratory Procedures Routinely Performed in Hospitals*

Following a discussion of the practice, by some hospitals, of routinely performing certain laboratory procedures on all admitted patients, the Council took a policy position— to be publicized in the CMA Medical Staff Bulletin.

ACTION: Voted to adopt the policy that the extent of laboratory procedures required when a patient enters a hospital should be a matter of judgment and decision by the attending physician and the medical staff.

35. *Public Law 89-239*

President MacLaggan and Immediate Past-President Teall reviewed CMA's participation in California implementation of Public Law 89-239 with particular reference to the work of the statewide California Committee on Regional Medical Programs. Scientific Board Chairman Longmire presented a recommendation that an advisory committee composed of Scientific Board members be appointed to consult with CMA Representatives to the California Committee on Regional Medical Programs.

ACTION: Voted to ask the Committee on Nominations of the Scientific Board to appoint (in consultation with the Committee on Committees) acting members of the advisory committee—to function until consideration and approval of the nominations at the October Council meeting.

36. *CMA Relationship with Component Societies*

Following a discussion of the relationships between CMA and its component medical societies, the Council decided that the matter needed further attention.

ACTION: Voted to establish an ad hoc committee to look into relationships between CMA and its component societies and to report back to the Council.

Councilors appointed to the ad hoc committee as as follows: Yant (chairman), Eastman, Kaiser, Miller and Taw.

37. *Future of UC, California College of Medicine*

After some discussion regarding the future location and affiliation of the College, the Council took the following step.

ACTION: Voted to send a letter re-emphasizing CMA's support of the College to the Board of Trustees of CCM and the UC Board of Regents, and to request CMA's President, President-Elect, and Council and Scientific Board Chairman to meet with these bodies to help in reaching a decision as to the future direction of the College.

38. *Cancer Commission Luncheon*

The Council received and considered a request from Doctor David A. Wood, chairman of the CMA Cancer Committee, for Council approval to sponsor a luncheon for members of the Cancer Commission of the American College of Surgeons.

ACTION: Voted not to approve co-sponsorship of the luncheon, on the basis of budgetary considerations.

Adjournment

There being no further business to come before it, the meeting was adjourned on Sunday, 18 September 1966, at 2:35 p.m. in the memory of Douglas Morrison, son of President-Elect Morrison.

CARL E. ANDERSON, M.D., *Chairman*
HELEN B. WEYRAUCH, M.D., *Secretary*

Constitutional Amendments

FOR ACTION IN 1967

Six constitutional amendments were introduced in the 1966 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

The proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before they come before the House of Delegates for action.

* * *

CONSTITUTIONAL AMENDMENT NO. 1-66

PHYSICIANS' BENEVOLENCE FUND

Introduced by: Council

Resolved: That Article IV, Section 6, of the Constitution of the CMA be amended by adding the language in italics and deleting the language shown in parentheses so it shall read:

"Section 6.—Physicians' Benevolence Fund

"The Council shall determine from year to year, at the time of the Annual Meeting, (at least $1.00 out of) *the portion* of the annual dues paid by each active member of the Association (shall) *to* be allocated to the Physicians' Benevolence Fund, Inc., a corporation. (and) *Funds so allocated* shall be used for the purposes as set forth in that corporation's articles and bylaws."

* * *

CONSTITUTIONAL AMENDMENT NO. 2-66

COMPOSITION OF THE COUNCIL

Introduced by: Council

Resolved: That Article III, Part B, Section 9, of the California Medical Association Constitution, be deleted and the following amendment be adopted:

"The Council shall consist of:

"(a) Elected councilors from the councilor districts set forth in Section 10. Each councilor district shall be entitled to elect one (1) councilor for each 1,000 active members, or major fraction thereof, according to its membership as of the first day of September of the preceding year; provided, that each councilor district shall be entitled to a minimum of one (1) councilor.

"(b) Elected councilors from any one district shall not, at any time, exceed 40 per cent of the total Council membership.

"(c) The president, president-elect, immediate past president, speaker and vice-speaker.

"(d) The secretary and editor, when they are members of the Association, and one member of the Executive Committee of the Scientific Board, who shall be elected by the Executive Committee of that body from representatives of the scientific sections or members-at-large. These three persons shall be ex officio members of the Council without the right to vote."

* * *

CONSTITUTIONAL AMENDMENT NO. 3-66

OFFICERS

Introduced by: Council

Resolved: That Article VI, Section 1, of the Constitution of the California Medical Association be amended by adding the language in italics and deleting the language shown in parentheses so that it shall read:

"Section 1.—Officers

"The officers of this Association shall be a President, a President-Elect, (a Secretary) *a Chairman of the Council, a Vice-Chairman of the Council,* a Speaker of the House of Delegates, a Vice-Speaker of the House of Delegates *and, when they are members of the Association, a Secretary and an Editor."*

CONSTITUTIONAL AMENDMENT NO. 4-66

CONSTITUTIONAL AMENDMENT TRANSFERRING AMADOR COUNTY TO FIFTH DISTRICT

Introduced by: Tenth District

WHEREAS, Article II, Part B, Section 10 of current CMA Bylaws places Amador County in Councilor District Number Ten; and

WHEREAS, only two of the 12 medical doctors licensed in Amador County maintain county society affiliation in a Tenth District society, the majority, because of travel patterns and hospital locations, preferring to affiliate with a county medical society in the Fifth District; and

WHEREAS, the Fifth and Tenth District delegations have endorsed such transfer of Amador County to the Fifth District; now, therefore, be it

Resolved: That Article II, Part B, Section 10 of the Constitution of the CMA be amended by adding the words in italics and deleting the words in parentheses, and to read:

"District Number Five, comprising *Amador,* Kern, Kings, Tulare, Fresno, Madera, Mariposa, Merced, Stanislaus, San Joaquin, Calaveras and Tuolumne Counties.

"District Number Ten, comprising Sacramento, (Amador,) Alpine, El Dorado, Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou Counties."

* * *

CONSTITUTIONAL AMENDMENT NO. 5-66

ESTABLISHING A SEPARATE COUNCILOR DISTRICT FOR THE COUNTY OF ORANGE

Introduced by: Orange County Medical Association

Resolved: That Article III, Part B, Section 10, Councilor District of the CMA Constitution be deleted and the following Section 10 substituted therefor.

"There are 12 districts as follows:

"District Number One, comprising San Diego.

"District Number Two, comprising Imperial, Riverside, San Bernardino, Mono and Inyo Counties.

"District Number Three, comprising Orange County.

"District Number Four, comprising the County of Los Angeles.

"District Number Five, comprising Ventura, Santa Barbara and San Luis Obispo Counties.

"District Number Six, comprising Kern, Kings, Tulare, Fresno, Madera, Mariposa, Merced, Stanislaus, San Joaquin, Calaveras and Tuolumne Counties.

"District Number Seven, comprising Monterey, San Benito, Santa Cruz, Santa Clara and San Mateo Counties.

"District Number Eight, comprising San Francisco County.

"District Number Nine, comprising Alameda County and Contra Costa County.

"District Number Ten, comprising Marin, Solano, Napa, Sonoma, Lake, Mendocino, Humboldt and Del Norte Counties.

"District Number Eleven, comprising Sacramento, Amador, Alpine, El Dorado, Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou Counties.

"District Number Twelve, consisting of any society which is not limited as to geographical area, or the area of which overlaps the area covered by one or more existing component societies; such society and its members shall not be considered to be members of any other councilor district."

* * *

CONSTITUTIONAL AMENDMENT NO. 6-66

REVISION OF DISTRICT ONE

Representing: Imperial
Introduced by: Burke E. Schoensee

Resolved: That Article III, Part B, Section 10 of the Constitution be amended by revising District Number One to include San Diego and Imperial Counties, and that Imperial County be deleted from District Number Two, and that otherwise said Section remain unaltered.

In Memoriam

Allen, Albert, San Pedro. Died 17 June 1966, in Long Beach, aged 79. Graduate of the University of Illinois College of Medicine, Chicago, 1912. Licensed in California in 1912. Doctor Allen was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Belisle, Rex C., Escondido. Died 11 September 1966, in Escondido, aged 40. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1949. Licensed in California in 1954. Doctor Belisle was a member of the San Diego County Medical Society.

✣

Benson, Kenelm Winslow, Berkeley. Died 3 October 1966, in Berkeley, aged 57. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1934. Licensed in California in 1939. Doctor Benson was a member of the Alameda-Contra Costa Medical Association.

✣

Carroll, William Adrian, San Francisco. Died 16 September 1966, aged 65. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor Carroll was a member of the San Francisco Medical Society.

✣

Cherry, Walter Smith, Rialto. Died 22 September 1966, in Los Angeles, aged 85. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1905. Licensed in California in 1924. Doctor Cherry was a member of the San Bernardino County Medical Society.

✣

Doren, Neil C., Los Angeles. Died 22 September 1966, in Ogdensberg, New York, aged 66, of cerebral vascular accident. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1947. Licensed in California in 1947. M.D. degree from California College of Medicine, 1962. Doctor Doren was a member of the Los Angeles County Medical Association.

✣

Francis, Raymond T., Santa Ana. Died 8 September 1966, in Santa Ana, aged 74. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1916. Licensed in California in 1919. Doctor Francis was a member of the Orange County Medical Association.

✣

Glogauer, Otto L., Long Beach. Died 26 September 1966, in Long Beach, aged 65, of acute myocardial infarction. Graduate of Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia, Germany, 1925. Licensed in California in 1942. Doctor Glogauer was a member of the Los Angeles County Medical Association.

✣

Henley, R. Bruce, Oakland. Died 27 August 1966, aged 56. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1937. Licensed in California in 1937. Doctor Henley was a member of the Alameda-Contra Costa Medical Association.

✣

Kasper, Raymond J., Fresno. Died 11 July 1966, in Salt Lake City, Utah, aged 57. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1933. Licensed in California in 1942. Doctor Kasper was a member of the Fresno County Medical Society.

✣

Keller, Samuel H., Riverside. Died 17 September 1966, aged 75. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1917. Licensed in California in 1920. Doctor Keller was a retired member of the Riverside County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

King, Gordon G., San Francisco. Died 25 August 1966, in San Francisco, aged 68. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1942. Licensed in California in 1942. Doctor King was a member of the San Francisco Medical Society.

✣

Lindenberg, Fred, Los Angeles. Died 22 September 1966, in Los Angeles, aged 75, of rupture of abdominal aorta. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1919. Licensed in California in 1924. Doctor Lindenberg was a member of the Los Angeles County Medical Association.

✣

Mendelsohn, Howard Abraham, Beverly Hills. Died 15 September 1966, in Los Angeles, aged 55, of coronary artery disease. Graduate of the University of Southern California School of Medicine, Los Angeles, 1936. Licensed in California in 1936. Doctor Mendelsohn was a member of the Los Angeles County Medical Association.

MYERS, R. (RUDOLPH) B. S., Santa Monica. Died 6 September 1966, in Santa Monica, aged 56, of arteriosclerotic heart disease. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1938. Licensed in California in 1940. Doctor Myers was a member of the Los Angeles County Medical Association.

✣

NORCROSS, HOWARD B., Los Angeles. Died 25 September 1966, in Los Angeles, aged 62. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Doctor Norcross was a member of the Los Angeles County Medical Association.

✣

SALE, J. JUDSON, San Francisco. Died 3 September 1966, aged 73. Graduate of the Medical College of Virginia, Richmond, 1917. Licensed in California in 1924. Doctor Sale was a member of the San Francisco Medical Society.

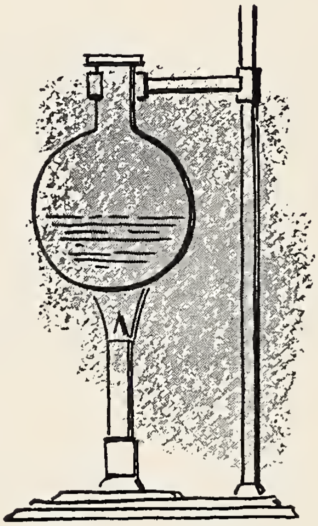
SCHILLINGER, ROBERT J., Los Angeles. Died 2 September 1966, in Palos Verdes Estates, aged 53. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1940. Licensed in California in 1940. Doctor Schillinger was a member of the Los Angeles County Medical Association.

✣

TROTT, LESLIE DENYSE, Glendale. Died 14 September 1966, in Glendale, aged 84, of cerebral vascular accident. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1915. Licensed in California in 1915. Doctor Trott was a member of the Los Angeles County Medical Association.

✣

WILLIAMS, EDWARD KARL, San Mateo. Died 8 September 1966, aged 43. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1951. Licensed in California in 1955. Doctor Williams was a member of the San Mateo County Medical Society.



application for HOTEL ACCOMMODATIONS

NINETY-SIXTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • APRIL 15-19, 1967

BILTMORE HOTEL, LOS ANGELES

House of Delegates Opening Session Saturday evening, April 15; Scientific Programs begin Sunday morning, April 16.

1. Fill in the form below **completely** for room accommodations at the CMA's 1967 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, 693 Sutter Street, San Francisco, California 94102.
4. **DEADLINE** for housing: April 1, 1967.

HOTEL ROOM RATES*

	Single	Double and Twins	Suites
BILTMORE HOTEL			
515 So. Olive Street	10.50-17.50	15.50-21.50	30.00-55.00
MAYFLOWER HOTEL			Triples
535 So. Grand Avenue	8.50-13.50	12.00-17.50	22.00
STATLER-HILTON			Suites
930 Wilshire Boulevard	11.00-17.50	16.00-22.50	30.00-65.00

*Rates subject to change

Send to: California Medical Association—*Housing Bureau*
693 Sutter Street, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1967 Annual Session in Los Angeles, April 16-19, 1967. The first meeting of the House of Delegates begins Saturday evening, April 15; Scientific Programs begin April 16.

Single Bedroom $.................... Twin-Bedded Room $.................... Double Bedroom $....................

Small Suite $.................... Large Suite $.................... Other $....................

First Choice Hotel.................... Second....................

Arrival (date) .... Hours.................... a.m. p.m. Departure (date) .... Hour.................... a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of both persons for each twin-bedded or double room, and names and addresses of all other persons for whom you are requesting reservations.

....

....

....

....

—PLEASE PRINT—

Your Name .... Officer? .... Delegate? .... Alternate? .... Speaker? ....

Address .... County ....

City and State.................... Zip No. ....

Plan NOW to Attend

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

ADVANCES IN DIAGNOSTIC TECHNIQUE

Capability • Reliability • Integration

Renowned speakers are:

- **William Arthur Altemeier, M.D., Chief**
  Department of Surgery
  University of Cincinnati College of Medicine
  Cincinnati
- **Irvine H. Page, M.D., Director**
  Research Center, Cleveland Clinic
  Cleveland
- **Herbert M. Stauffer, M.D., Professor and Chairman**
  Diagnostic Section, Department of Radiology
  Temple University Science Center
  Philadelphia
- **Jon V. Straumfjord, Jr., M.D., Professor and**
  Chairman, Department of Clinical Pathology
  University of Alabama, Medical College
  Birmingham
- **George Zur Williams, M.D., Chief**
  Clinical Center, National Institutes of Health
  Bethesda

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS

SPECIAL CONFERENCES INCLUDE:

Cancer of the Colon and Rectum
Research Advances in Veterinary Medicine
The Impact of Medicare—Titles 18 and 19
Medicine and Religion—Moral Aspects of New Procedures

PLUS OUTSTANDING SCIENTIFIC AND TECHNICAL EXHIBITS

PUBLIC HEALTH REPORT

Lester Breslow, M.D., M.P.H.
Director, State Department of Public Health

A REVIEW COMMITTEE has recommended sites for the establishment of two regional dialysis centers for the treatment of patients with chronic uremia. The group has recommended the centers be located in San Francisco General Hospital and the Los Angeles County General Hospital.

Initially, dialysis services will be provided at each facility for 30 patients in the hospital and 20 patients living at home. At the centers, training will be given to medical and nursing personnel who will carry out dialysis services in other parts of the state. Close cooperation with other medical specialists who are seeking ways to develop successful means of kidney transplantation will be developed and maintained.

The Legislature in its last session authorized the State Health Department to establish the regional centers, with the Bureau of Chronic Disease responsible for implementing the program. The two institutions were recommended in compliance with terms of the legislation authorizing the centers—that they be located in a metropolitan area and have affiliation with a large hospital that has a full range of medical, surgical and rehabilitative services.

Site visits will be made shortly by teams representing the State Departments of Public Health and Rehabilitation, an outstanding authority in chronic hemodialysis, a member of the Review Committee and a person expert in financial matters.

The teams will determine whether the recommended institutions can develop dialysis centers as described in the legislation. As soon as approval of the centers by the site teams is given, final negotiations between the prospective centers and the two state departments will be completed.

The centers will be established and become operational as soon as possible. Announcement will be made in CALIFORNIA MEDICINE just before the centers begin to accept patients.

The State Health Department has just completed its new Data Processing Center in quarters located at 2120 Berkeley Way, Berkeley, where it has a Spectra 70 Computer and a staff of 70.

The new machine is one of the first of the new generation of computers to be installed in the San Francisco Bay Area. These machines are many times more powerful than the famous UNIVAC I which was the wonder of the scientific world only a dozen years ago.

Spectra 70 will be used for operations throughout the department, but its biggest job will be in work toward the improvement of medical care for Californians. It will also be used in air pollution studies, vital statistics and cancer research studies.

Before acquiring its own machine, the department since 1959 had used the computers at the University of California for studies into the causes of cancer, heart disease and other health problems.

WOMAN'S AUXILIARY

to the California Medical Association

If your wife has told you of the Los Angeles Poinsettia Ball, the amount of money raised in California last year for AMA-ERF, the new book, "Our Gems Are Jewels," and the activities planned for the wives at the California Medical Association convention next April — if she has told you of these things, you can be pretty sure that she has read *Courier,* the publication of the Woman's Auxiliary to the California Medical Association, sent four times a year to all paid-up members.

The Summer issue carries a report of the Spring convention, announcement of the Annual AMA meeting, biography and picture of the newly installed State President and accounts of certain County projects that have taken place during the Winter and Spring. In the Fall issue one can read a brief biographical sketch and view the picture of each State Board member and County President. For the stay-at-home, there is an account of the AMA convention by the State President-elect, and the reader is introduced to the new National President—this year, Mrs. Asher Yaguda of New Jersey. The Winter issue contains the committee reports of the State Chairmen, and an outline of the County Auxiliary programs planned for the year. The Spring number is the Annual Convention Issue, and it contains more articles concerning activities in the County Auxiliaries that have occurred during the Fall. Each issue contains a message from the State President, as many pictures as possible and articles of other general interest, as space permits.

The CMA underwrites the cost of these four issues, which cost around $6,000 to $6,500 yearly. There is an editor and co-editor, and two circulation managers from the Auxiliary who all work in close cooperation with Jack Collins, CMA staff liaison to the Auxiliary, in the production of the magazine. At present our circulation is around 9,500. If the wives of all physicians in California joined the Auxiliary, the circulation would more than double.

At the WACMA Fall conference in September 1966 the State Board gave approval to carrying advertising in *Courier,* provided it was financially feasible. This matter is being looked into by the advertising department of California Medicine, which would handle this phase of production.

If advertising does prove to be a profitable venture, we hope to use more feature stories, color, and professional photographers and artists. The future may see a California version of the National Auxiliary publication, *M.D.'s Wife.*

One final word, doctors! All who receive *Courier* also receive your CMA *Newsletter* once a month. As the *Courier* addressograph plates are used for the mailing of *Newsletter* to Auxiliary members, it is mailed to the home address, so we don't have to rely on our husbands' bringing it home from the office!

M.D.'s Wife, the *Courier* and the CMA *Newsletter* go to all Auxiliary members. Thus, a Medical Auxiliary member is an informed wife of a doctor!

Mrs. Harry Alton
Editor, *Courier*

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. Forest Grunigen, Los Angeles, received "The Award of Achievement and Service" from the Associated Alumni of the California College of Medicine at the group's annual convention held recently in Coronado.

Dr. Walter Hopps, past-president of the alumni association said, "This award, being presented for the first time, is in recognition of Dr. Grunigen's outstanding achievements in his medical specialty, his leadership in the historic merger of the two professions of medicine in California and his tireless efforts in helping the California College of Medicine to become an integral part of the University of California system."

Dr. Grunigen took a leading part in the professional and legislative action that in 1962 unified the osteopathic and medical professions in California. He is currently a member of the California Board of Medical Examiners and a Councilor of the California Medical Association.

SAN FRANCISCO

The sixth **Sterling Bunnell Memorial Lecture on Reconstructive Surgery** will be presented by Sir Herbert Seddon of the Royal National Orthopedic Hospital, Long, England, Friday, 13 January 1967, in conjunction with the 22nd annual meeting of the American Society for Surgery of the Hand, at the Jack Tar Hotel, San Francisco. The title of Sir Herbert's address is "Peripheral Nerve Injuries of the Upper Extremity."

GENERAL

Robert J. Koch has been appointed executive vice-president of **California Physicians' Service.** Mr. Koch was formerly director of marketing administration for the data processing division of Honeywell in Wellesley Hills, Mass.

In making the announcement, Thomas C. Paton, president of CPS, pointed out that Koch has had over 22 years' experience in the field of prepaid health coverage with Michigan Blue Cross and Blue Shield.

Mr. Koch is a member of the American Management Association and has been a frequent speaker at the association's seminars. He has taught graduate courses in management administration at Wayne State University, and is a graduate of Notre Dame.

* * *

A new schedule of Maximum Allowances for clinical laboratory services is now in effect for the California Medical Assistance Program (Medi-Cal). The new schedule is retroactive to 1 September and provision is made for rolling back billings that may have been made in the meantime at the old rates. The maximum fees of the schedule are higher than those of the previous schedule. They were arrived at by applying a $5 conversion factor to the Laboratory Procedures section of the *Relative Value Studies, 1964*. These maximums apply to billings from both physicians and licensed laboratories.

Services rendered to Medi-Cal patients are to be charged at the usual fees charged other patients. Payment will be made up to the maximums of the new schedule.

Five additional laboratory procedures have been added to the state schedule:

Procedure Number	*Description of Procedure*	*Value*
8720	Serum Phenylaline	$ 2.50
8970	Chromosomal analysis	75.00
8972	Nuclear chromatin count (buccal smear)	5.00
8975	Sweat test—skin chlorates—by silver nitrate agar method	5.00
8976	Collection of sweat	5.00

The Schedule of Maximum Allowances does not apply to those procedures which only a physician such as a pathologist may lawfully perform. Bills for such services may be based on a physician's usual charge. These include the following procedures which are shown in the laboratory section of *Relative Value Studies, 1964,* but not in the state schedule.

Procedure Number	*Description of Procedure*	*Value*
8634	Bone marrow, collection and examination of material	5.0 units
8636	Examination of material only	3.0 units
8638	Bromsulphalein (BSP)	1.5 units
8911 thru 8925	(Tissues section)	Various units

(Note: 8901 through 8908, Autopsies, are not paid for under this plan.)

Anyone who has billed substantial amounts for laboratory services performed since 1 September, and whose usual fee for such services exceeded a $4 unit value on the *Relative Value Studies,* may submit claims for the differences as allowed by the new schedule of maximum allowances.

* * *

Ten clinical fellowships and one advanced clinical fellowship have been awarded by the **American Cancer Society** for study at seven California institutions.

The purpose of these fellowships is to provide **postgraduate training in cancer** for physicians and dentists.

The awards made in California are part of a group of 236 fellowships in 34 states and Puerto Rico.

The special training enables the doctors to help their communities by sharing their advanced knowledge with other physicians and dentists through local hospitals, tumor boards and professional societies.

The California awards are for study at the following institutions: Cedars-Sinai Medical Center, Los Angeles; Los Angeles County Harbor General Hospital; Presbyterian Medical Center, San Francisco; Stanford University School of Medicine, Palo Alto; University of California at Los Angeles School of Medicine; University of California San Francisco Medical Center School of Medicine; and University of California San Francisco Medical Center School of Dentistry.

Since the beginning of the program of clinical fellowships, the American Cancer Society has invested more than $10 million in the training of nearly 2,250 physicians and dentists.

* * *

The West Coast Allergy Society will hold its annual scientific sessions 1 to 3 December at the Flamingo Hotel, Las Vegas, Nevada.

* * *

The annual meeting of the **American Academy of Forensic Sciences** will be held 20 to 25 February 1967, at the Princess Kaiulani Hotel in Honolulu.

The Academy was founded in 1948 to centralize the various disciplines of the forensic sciences in order to promote the use of scientific methods and knowledge in the solutions of legal problems and controversies; to improve professional qualifications of scientists engaged in the assistance of the courts and attorneys; and to develop and extend a better understanding of the application of legal doctrines to scientific professions.

The Academy encompasses the disciplines of toxicology, pathology, psychiatry, questioned documents, criminalistics and forensic jurisprudence. Membership consists of more than 700 leaders in these forensic fields.

As host for the meeting, Alvin V. Majoska, M.D., has issued an invitation to all those interested in such disciplines. Further information and copies of the scientific program may be obtained by writing to Dr. Majoska at the Office of the Medical Examiner, City and County of Honolulu, 1455 South Beretania Street, Honolulu, Hawaii 96814.

The Physician's BOOKSHELF

TODAY'S DRUGS—Specially Commissioned Articles from the British Medical Journal, Published Between January 1963 and April 1964. Grune & Stratton, Inc., New York, 1965. 400 pages, $5.50.

The physician of today is presented with advice on recent advances in drug therapy from a variety of sources. In the United States counsel by teachers of medicine has been supplemented and to some extent supplanted by the exhortations of the pharmaceutical house. In England politics as well as big business has entered the competition. This book, which is based on a series of review articles published by a number of different contributors in the *British Medical Journal* in 1963 and 1964, is designed to give useful and medically authoritative advice on the treatment of patients. The *Journal* commissioned these articles to assess the value of new remedies and to compare them with older medications in order to form a clear and up-to-date review of drug treatment.

Through the greater part of the book the editors have been successful in accomplishing their purpose. Good, solid information is presented in compressed form. The contents are divided into 11 general parts with several chapters in each. In most chapters there is a general review of the therapeutic subject with the considered opinion of the authors on each group of drugs stated in authoritative and succinct fashion. Most chapters contain a table listing the individual drugs in the chapter with their generic and proprietary names and their dosage.

As noted in reviews of other British medical texts dealing with advances in therapy, there are two principal drawbacks to this volume: (1) Differences in British and American terminology for the same drug are often confusing and may keep the reader from recognizing the product. (2) At the time the text is published, the British volume is several years behind the comparable American book. On the other hand, the medical student or practitioner wanting an extra clear, succinct, authoritative reference will do well to have this book at hand.

E. WAYBURN, M.D.

* * *

HANDBOOK OF CARDIOLOGY FOR NURSES—Fifth Edition—By Walter Modell, M.D., F.A.C.P., Doris R. Schwartz, M.A., R.N., Louise S. Hazeltine, M.A., R.N., and Frederic T. Kirkham, Jr., M.D. Springer Publishing Company, Inc., New York, 1966. 323 pages, $4.75.

This handbook is in its fifth edition and is an excellent treatise not only for the nurse but for paramedical individuals who wish to know more about heart disease. The text is clearly and simply written and not only emphasizes new work, but also highlights the activities in which nurses can be helpful. This is particularly clearly stated in the chapter on coronary artery disease.

The book is brief but comprehensive, and in addition to covering the usual types of heart disease, discusses anatomy, physiology and patho-physiology, resuscitation, the coronary care unit and cardiac surgery. There is a brief but clear account of the drugs used in heart disease and practical suggestions for low sodium and low fat diets. Of special note is the up-to-date bibliography at the end of each chapter, again with special reference to the role of the nurse, but with enough references pertaining to the disease to broaden the perspective.

The fact that a new edition has been written approximately every four years attests the usefulness of the book. The experience of the medical and nursing authors is clearly shown in the book. It is highly recommended.

MAURICE SOKOLOW, M.D.

* * *

LITTLE STROKES—By Walter C. Alvarez, M.D., D.Sc., Emeritus Professor of Medicine, University of Minnesota (Mayo Foundation). Foreword by Michael E. DeBakey, M.D. J. B. Lippincott Company, Philadelphia and Toronto, 1966. 190 pages, $8.00.

As the author writes, "This little volume is unique." It is an expression of his interest over many years and a formulation of his thinking on a condition with many manifestations and many names which affects patients of generalists and specialists alike. Dr. Alvarez is a gastroenterologist who long ago found that he "must be somewhat of a neurologist and a psychiatrist."

This is Dr. Alvarez's thesis: In the majority of people who have rather abruptly deteriorated in judgment, memory, initiative, endurance, and poise, it is possible to bring out a history of one or more transient lapses of cerebral function (small strokes), minor so far as classical neurological defects are concerned yet disastrous to total functioning.

The nature of the author's practice has precluded his furnishing any new pathological observations, but he has furnished ample bibliographical references. His case reports are in the form of sketches, very readable but admittedly somewhat discursive and anecdotal.

CLARENCE W. OLSEN, M.D.

* * *

MEDICAL CARE OF THE ADOLESCENT—Second Edition—By J. Roswell Gallagher, M.D., Chief, The Adolescents' Unit, Children's Hospital Medical Center; Clinical Professor of Pediatrics, Harvard Medical School, Boston; with eight contributing authors, and The Staff Physicians of the Adolescents' Unit. Appleton-Century-Crofts (Division of Meredith Publishing Company), New York, 1966. 489 pages, $12.00.

In 1960, it was the privilege of this reviewer to comment on the first edition of Gallagher's book *Medical Care of the Adolescent*. At that time I was most impressed with the breadth of coverage of all medical problems relevant to the adolescent, and especially with the consistent integration of psychologic with physiologic insights. The conclusion of my review at that time was: "Altogether the book is a unique, stimulating and reassuring guide to anyone interested in caring for adolescents and their problems."

The popularity of the book is indicated by the fact that only six years later a second edition has been published. The new edition not only has an increase from 369 to 489 pages, but also has a number of added chapters on other clinically important problems, written by various authors. Among these the following may be mentioned: Chapter 4: Secular Acceleration of Height and Biologic Maturation, by Thomas E. Cone, Jr.; Chapter 17: Venereal Disease, by Gallagher; Chapter 22: Headache, by Simeon Locke; Chapter 25: Surgical Problems, by Samuel R. Schuster; and Chapter 29: Juvenile Rheumatoid Arthritis, by Thomas E. Cone, Jr.

These additions will ensure and enhance the value of this pioneering work.

LEONA M. BAYER, M.D.

* * *

PROGRESS IN CLINICAL CANCER—Volume II—Edited by Irving M. Ariel, M.D., F.A.C.S., Associate Clinical Professor of Surgery and Attending Surgeon, New York Medical College, Flower and Fifth Avenue Hospitals; Attending Surgeon and Chief of the Soft Somatic Tissue Tumor Service, Hospital for Joint Diseases; Attending Surgeon, Pack Medical Group, New York, N.Y. Grune & Stratton, Inc., New York, N.Y., 1966. 375 pages, $15.75.

This monograph is divided into the following sections: General Considerations, Diagnosis, Surgery, Irradiation, Chemotherapy, and Specific Neoplasms.

In the year 1966, it would be timely to stress "diagnosis in the useful period." We know, alas, that the diagnosis of most bronchial cancers, esophageal cancers, and gastric cancers cannot be made in the useful period, that is, the period before the tumor has disseminated. The usual time of clinical recognition of cancer is in the last 20 per cent of the lifetime of that given cancer.

The articles on the use of hyperbaric oxygen in conjunction with radiotherapy or chemotherapy are properly conservative. The absence of clinical controls is of course a stumbling block.

Humphrey has a commendably candid article on the treatment of primary bronchial cancer.

The monograph is well-illustrated and indexed.

L. H. GARLAND, M.D.

* * *

SPONTANEOUS REGRESSION OF CANCER—A Study and Abstract of Reports in the World Medical Literature and of Personal Communications Concerning Spontaneous Regression of Malignant Disease—By Tilden C. Everson, M.D., Ph.D., F.A.C.S., Clinical Professor of Surgery, University of Illinois College of Medicine, and Warren H. Cole, M.D., F.A.C.S., F.R.C.S. (Eng., Hon.), F.R.C.S. (Edin., Hon.), Professor of Surgery and Head of the Department of Surgery, University of Illinois College of Medicine. W. B. Saunders Company, Philadelphia, 1966. 560 pages, $20.00.

This interesting and well-illustrated monograph deals with reported examples of spontaneous regression of human cancer. After an introductory chapter, there are a series of 15 chapters dealing with regressions in specific sites. These are followed by chapters dealing with prolonged arrest of cancer, and long delayed metastasis of cancer.

The authors stress the fact that by regression they mean just that; they do not imply regression to complete disappearance of tumor nor cure.

They reportedly studied the world literature since 1900 and also acquired some cases by personal communication. From this enormous number of cancer cases, they consider 176 to be fairly well documented. Of considerable interest is the fact that more than half of this group are confined to four types of cancer: adenocarcinoma of the kidney (hypernephroma), neuroblastoma, malignant melanoma, and choriocarcinoma. Spontaneous regression of cancer was much less frequent in the common sites such as: colon, breast, uterus and lung.

In 35 of this small number of cases the regression lasted more than five years. Not infrequently, autopsy disclosed persistent cancer in cases otherwise thought to be examples of regression.

The reason for the bona fide cases is, of course, not known. Hormonal factors are probably the leading cause.

L. H. GARLAND, M.D.

ROENTGEN SIGNS IN CLINICAL PRACTICE—Vol. I, Basic Principles and Radiology of the Skeletal System (pp. 1 to 718); **Vol. II, Radiology of the Chest, Genitourinary System and Gastrointestinal Tract** (pp. 719 to 1831) —By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina; formerly Professor and Head of the Department of Radiology, University of Arkansas School of Medicine, Little Rock, Arkansas. With the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia), M.D., Research Associate, Department of Radiology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. W. B. Saunders Company, Philadelphia, 1966. The set of 2 volumes, $38.00. Volume I singly, $18.00; Volume II singly, $20.00.

This new edition arrives approximately 10 years after the first one. It has been expanded to two volumes and includes over 700 additional pages. The purpose remains as before: systematic presentation of diagnostic radiography as it relates to the clinical practice of medicine.

The general style and format are continued as in the first edition. There are many excellent tables and diagrams. The authors clearly state that they do not attempt to encompass adequately all the various nuances of present-day radiology.

The new two-volume edition is recommended especially for students and residents interested in correlating the uses and limitations of diagnostic radiology with clinical disease.

J. H. HEALD, M.D.

* * *

RADIOGRAPHIC ATLAS OF THE GENITOURINARY SYSTEM—By Charles Ney, M.D., and Richard M. Friedenberg, M.D. (with contributing authors). J. B. Lippincott Company, Philadelphia, 1966. 741 pages, $36.00.

A big comprehensive and visually attractive atlas of 741 pages containing at least one example of clinically encountered urologic disorders.

The authors, in collaboration with a very competent group of contributing authors, have brought out the newest methods of investigation in a clear and usable form.

The illustrations are necessarily somewhat small and grainy, but by placing them to the margins of the page adequate descriptive material alongside each picture has been included, so that correlation is easy. One might wish for more information here on differential diagnosis, by notations covering the significant changes depicted in the illustration.

The text, which has been suitably kept to a minimum, is clear and references adequate. The index is incomplete (i.e., "Backflow *See* Reflux, vesico-ureteral"). The price is appreciable, but the volume is worth a lot to the practicing urologist and for the teaching of the house staff.

* * *

ANNUAL REVIEW OF MEDICINE—Vol. 16—By Arthur C. De Graff, Editor, New York University College of Medicine; and William P. Creger, Associate Editor, Stanford University School of Medicine. Annual Reviews, Inc., Palo Alto, Calif., 1965. 473 pages; and

ANNUAL REVIEW OF MEDICINE, Vol. 17, 1966—By Arthur C. De Graff, Editor, New York University College of Medicine; and William P. Creger, Associate Editor, Stanford University School of Medicine. Annual Reviews, Inc., Palo Alto, Calif., 1966. 563 pages. The price, postpaid, for the current and all back volumes of the Annual Review of Medicine is $8.50 per copy (U.S.A.) and $9.00 (elsewhere). (California residents subject to 4 per cent sales tax.) Student rate information available.

The Annual Review of Medicine continues to be a valuable source of accurate reference information for the medical practitioner and student interested in keeping up with the progress of medicine in a variety of fields.

The editorial committee does not attempt to review the advances in all aspects of medicine each year but concentrates on those areas in which substantial progress has been made. It obtains as contributors scientific investigators who have themselves been partly responsible for these advances. For 1965, 24 subjects are reviewed and for 1966, 31 subjects. Although they vary widely in content and treatment they are generally very well done.

Both volumes can be recommended to physicians and students wishing to keep as close as possible to the current investigative level of any subject.

Edgar Wayburn, M.D.

* * *

SYMPOSIUM ON SURGERY OF THE OCULAR ADNEXA—Transactions of the New Orleans Academy of Ophthalmology—By Arthur Gerard DeVoe, M.D.; Sidney A. Fox, M.D.; Howard Naquin, M.D.; T. E. Sanders, M.D.; Byron Smith, M.D.; Everett R. Veirs, M.D.; and Joseph A. C. Wadsworth, M.D. The C. V. Mosby Company, St. Louis, Mo., 1966. 245 pages, $16.00.

This book is a compilation of the lectures from the Symposium on Surgery of the Ocular Adnexa given at the Fourteenth Annual Session of the New Orleans Academy of ophthalmology, 14 to 19 February 1965.

The authors are outstanding ophthalmologists in the various fields of their subjects. They have discussed the pathogenesis and diagnosis of each condition and have described the treatment that they have found most satisfactory by their own personal experience. Differences of opinion are brought out in the Round Table Discussions included in the back of the book.

The textbook consists of the following chapters:

1. Basic principles in ophthalmic plastic surgery (Byron Smith).
2. Reconstructive surgery for burns of the lid and brow (Byron Smith).
3. Reconstructive surgery for congenital and traumatic colobomata of the lids (Byron Smith).
4. Repair of entropion (Sidney A. Fox).
5. Repair of ectropion (Sidney A. Fox).
6. Correction of ptosis (Sidney A. Fox).
7. Conjunctival sac reconstruction after enucleation (Howard Naquin).
8. The lacrimal gland (T. E. Sanders).
9. Dacryocystography (Benjamin Milder and T. E. Sanders).
10. Congenital obstruction of the nasolacrimal drainage system (Everett R. Veirs).
11. Obstruction of the nasolacrimal drainage system in adults (Everett R. Veirs).
12. Management of traumatic lesions of the lacrimal drainage system (Everett R. Veirs).
13. Tumors of the lid and conjunctiva (Joseph A. C. Wadsworth).
14. Pathology of orbital tumors (Joseph A. C. Wadsworth).
15. The nonsurgical treatment of tumors of the ocular adnexa (Arthur Gerard DeVoe).
16. Surgical treatment of orbital tumors (Howard Naquin).
17. Exenteration of the orbit (Howard Naquin).
18. Other ophthalmic plastic procedures and various comments (Byron Smith).

The publishing of Symposium on Surgery of the Ocular Adnexa should be limited to the more outstanding ones. This one, in my opinion, does not qualify even though the members of the Symposium are quite well known.

THE PEDIATRICIAN'S OPHTHALMOLOGY—A collaborative effort of several authors—Edited by Sumner D. Liebman, M.D., Instructor in Ophthalmology, Harvard Medical School, Boston, Massachusetts, and Sydney S. Gellis, M.D., Professor and Chairman, Department of Pediatrics, Tufts University School of Medicine, Boston, Massachusetts. The C. V. Mosby Company, St. Louis, 1966. 352 pages, $19.50.

This textbook consists of the following chapters:

1. Anatomy of the eye (George M. Howard, M.D.).
2. Growth of the eye and development of vision (Marshall M. Parks, M.D.).
3. Methods of examination (Marshall M. Parks, M.D.).
4. Refraction (John S. McGavic, M.D.).
5. Strabismus (Frank D. Costenbader, M.D.).
6. External Diseases of the eye (James H. Allen, M.D.).
7. Internal diseases of the eye: Retinal detachment (Edward Okun, M.D.); Inflammatory diseases (Conrad L. Giles, M.D.); Degenerative diseases of the retina (J. Wallace McMeel, M.D.).
8. Ocular manifestations of pediatric systemic diseases (Trygve Gundersen, M.D., Sumner D. Liebman, M.D., and Steven M. Podos, M.D.).
9. Neuro-ophthalmology in children (David D. Donaldson, M.D., and Frank Walsh, M.D.).
10. Developmental and acquired cataracts of infancy and childhood (Frederick C. Cordes, M.D.).
11. Glaucoma in infancy and childhood (Paul A. Chandler, M.D.).
12. Diseases of the orbit (Arnold J. Kroll, M.D., and Virgil G. Casten, M.D.).
13. Neoplasms (Ira S. Jones, M.D.).
14. Trauma (Sidney A. Fox, M.D.).
15. Specific disability for reading (Reading dysphoitesis, John Money, Ph.D.).
16. Social and emotional aspects of ophthalmic problems (Madeline Shipsey, M.S., Helen Gibbons, M.S., and Milton A. Jahoda, M.S.).
17. Genetic applications to pediatric ophthalmology (Elsa D. Kertesz, M.D., and Harold F. Falls, M.D.).

This text is not designed for the ophthalmologist, who will find it too elementary, but for the pediatrician and general practitioner. The chapters are short and to the point and written in terms that can be understood by the ophthalmologically-uninitiated physician. It is hoped that this text will bridge the gap between general medicine and ophthalmology and it is highly recommended for those doctors who are interested in increasing their general knowledge of the eye.

R. M. Sinskey, M.D.

* * *

FINE-NEEDLE ASPIRATION BIOPSY—Used as a Direct Adjunct in Clinical Diagnostic Work—By Nils Söderström, M.D., Professor of Medicine, Lund. Grune & Stratton, Inc., New York, 1965. 159 pages of text and 79 pages of illustrations and legends, $16.00.

This book has been written to call attention to the potentialities of fine-needle aspiration biopsy by presenting the author's experience with approximately 6,000 such biopsies from most of the body's organs and tissues. The small caliber needle (less than 0.8 mm. outer diameter) which is used is considered to be much less hazardous than the larger needles used in the more common "punch" biopsies. The author's results, which include 265 spleen punctures in which no complications occurred, would appear to strongly support this claim. The specimen obtained by this procedure consists of a suspension of cells in tissue fluid which is smeared on a glass slide with the same technique used for preparing blood smears.

Although the techniques as well as the indications and contraindications for fine-needle aspiration biopsy are discussed, most of the book is devoted to a detailed description of the normal and abnormal cells found in aspirates from a variety of tissues in a number of different diseases. The author has approached the problems of cytologic biopsy from the point of view of a hematologist and has attempted to identify the aspirated cells with the precision commonly applied to bone marrow smears. However, he readily admits that such definite identification of many cells frequently can not be made with certainty. Furthermore, a considerable amount of effort and experience are required to develop such skills. In the author's words, "to be a method of value fine-needle biopsy demands highly competent examiners with special experience of this rather specific diagnostic method." The potential diagnostic accuracy of this technique would appear to be less than that of the routine hematological procedures, but greater than exfoliative cytology, which should be used to screen a large number of patients for lesions which can then be definitively diagnosed by microscopic examination of tissue obtained by standard biopsy procedures.

This book is lucidly written, although the names applied to some pathological conditions are somewhat ambiguous. Thirty-nine plates of illustrations are included, 13 of which are in color. Most of these illustrations are of only medium quality and are not fully adequate for a book in which illustrations are so vitally important. Many of the photomicrographs would be more helpful if they had been taken at a higher magnification. Although the color rendition is sometimes inaccurate, the frequent lack of clarity and detail is a greater handicap. The legends for the illustrations are occasionally confusing and some of the text references to particular photomicrographs appear to be erroneous. Finally, the location of the illustrations at the back of the book requires incessant shuffling back-and-forth, which is an aggravating nuisance. The bibliography, which contains 146 references, is described by the author as incomplete. However, its usefulness is further diminished by the failure to include titles for the articles which have been cited.

In summary, Dr. Soderstrom's monograph is quite interesting and contains a large quantity of detailed information. It would be helpful for anyone attempting to develop the highly specialized skills required to evaluate the specimens obtained by this technique.

JAMES A. WILKERSON, M.D.

SURGICAL APPROACHES TO THE NECK, CERVICAL SPINE AND UPPER EXTREMITY—By Emanuel B. Kaplan, M.D., formerly Associate Professor of Clinical Anatomy, College of Physicians and Surgeons, Columbia University, New York City; Consultant in Orthopedic Surgery, Director of Hand Surgery, Hospital for Joint Diseases, New York City; Consultant in Orthopedic Surgery, Bronx Lebanon Center, New York City, and St. Joseph's Hospital, Paterson, New Jersey. W. B. Saunders Company, Philadelphia, Pa., 1966. 246 pages, $11.50.

Dr. Kaplan has written this book with the surgeon in mind, discussing the surgical anatomy from the operative viewpoint rather than from the viewpoint of anatomical exposure.

Surgical approaches are described for various pathological conditions, and in some instances the best operation is discussed. The approaches are well illustrated by Robert Demares and the line drawings are very clear.

Some of the pitfalls in each approach are presented to aid the surgeon in avoiding these hazards. This book would be of value for the orthopedist, neurosurgeon, and general surgeon who operates in the neck or upper extremity. It is an excellent book to supplement other anatomical texts but does not replace them, as a good general knowledge of the anatomy of this area is of value to make best use of this book.

An excellent reference list is included at the back of the book for related reading.

LEONARD MARMOR, M.D.

* * *

OCULAR PHARMACOLOGY—By William H. Havener, B.A., M.D., M.S. (Ophth.), Professor, Department of Ophthalmology, Ohio State University, Columbus, Ohio; Member, Attending Staff, University Hospital, Columbus, Ohio; Member, Consulting Staff, Children's Hospital and Mt. Carmel Hospital, Columbus, Ohio. The C. V. Mosby Company, St. Louis, 1966. 456 pages, $21.75.

This book should be part of the office library of every ophthalmologist. Ophthalmology, in common with other specialties, has become "super-specialized" into subspecialties, each with its own pharmacopeia.

William Havener in this book gives an up-to-date practical reference book, with sufficient background of usable basic knowledge so that the student and practitioner alike may benefit.

Sufficient equal treatment is given to external disease management, systemic medications for infections, a large and excellent section on autonomic drugs, chelating agents and steroid therapy.

Much of the material was heretofore only obtainable by collecting reprints, reference to pertinent journals and personal notes. A need has been very adequately met.

ARTHUR JAMPOLSKY, M.D.

Fortify Nonfat Dry Milk, AMA Urges

Federal regulations should be modified to permit fortification of all nonfat dry milk with vitamins A and D, an American Medical Association council has urged.

Vitamin fortification would help prevent one of the possible paradoxes of food relief programs: that unless vitamins are also supplied, existing nutritional deficiencies can be made worse by supplementing vitamin-short diets with the protein, minerals, and calories in nonfat dry milk.

The AMA's Council on Foods and Nutrition has previously endorsed the fortification of nonfat dry milk. Its statement in the September 26 *Journal of the AMA* repeats this endorsement and encourages revision of the U.S. Public Health Service Milk Code to make fortification possible.

Some nonfat dry milk going overseas in the Food for Peace program already is fortified with vitamins A and D, the statement points out. This is made possible through a cooperative program between the Agency for International Development and the U.S. Department of Agriculture.

The Council urges that *all* nonfat dry milk be fortified and that the standards of identification for the substance, established by Congress in 1944, be changed to permit this.

"Nonfat dry milk is distributed widely as a surplus food commodity in domestic and foreign relief programs," the statement said. "It replaces fluid whole milk in the diet of entire families in the United States. Therefore, it is important that nonfat dry milk be equivalent in fat-soluble vitamin content to whole fluid milk. This is not now the case."

It has become commercially feasible to fortify dry milk with vitamins without affecting its taste or stability, the statement noted.

"Serious nutritional problems exist in many areas of the world. Emergency food relief programs of many kinds have made significant inroads. However, the availability of surplus farm commodities cannot be considered justification for their inclusion in relief programs unless the foods meet the specific needs of the recipient population," the statement said.

"An existing nutritional deficiency can be made more grave by supplementing a diet with foods lacking the nutrient in short supply. Quiescent inadequacies can become full-blown deficiencies if additional protein, minerals, and calories are provided in the absence of adequate vitamin intake. This could be anticipated with both vitamins A and D.

"The Council on Foods and Nutrition strongly recommends that all nonfat dry milk be fortified with the vitamins A and D. However, the stand-

(Continued on Page 34)

Little-known moments in history No. 1:

Mr. Ra, a sculptor was commissioned by Queen Nefertiti to do a statue of herself, and by King Tut to do a large lion for his front lawn. Confused by vertigo, Mr. Ra got the whole thing mixed up. Did he get a royal bawling-out!

Antivert® stops vertigo tablets-syrup

(meclizine HCl, nicotinic acid)

Tablets: (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.)
Syrup. (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.)

Most widely prescribed anti-vertigo agent[1]
Complete to moderate relief in 9 out of 10 patients[2]

Antivert, the leading anti-vertigo product,[1] combines meclizine HCl, an outstanding drug for treatment of vestibular dysfunction, with nicotinic acid, a drug of choice for prompt vasodilation. Prescribe Antivert for your patients with vertigo, Meniere's syndrome or allied disorders.

Precautions and contraindications: Frequent, short-lived reactions include: cutaneous flushing, sensations of warmth, tingling and itching, burning of skin, increased gastrointestinal motility, and sebaceous gland activity. In explaining these reactions to the patient, it is suggested that they be regarded as a desirable physiological sign that the nicotinic acid is carrying out its intended function of vasodilation. Because of this vasodilation, severe hypotension and hemorrhage are obvious contraindications to Antivert therapy. Although the incidence of drowsiness and other atropine-like side effects such as dry mouth and blurring of vision is low, the physician should alert the patient to the need for due precautions when engaging in activities where alertness is mandatory. **Use in pregnancy:** A review of available animal data reveals that meclizine exerts a teratogenic response in the rat. While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human fetus. Consequently, consideration should be given to initial use of a nonphenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum.

Dosage: One tablet or one to two teaspoonfuls (5-10 cc.) t.i.d. just before meals. Specific requirements for individual patients should be determined by the physician.

Supplied: Tablets in bottles of 100 and 500. Syrup in pint bottles. Rx only.

References: 1. Based on 1965 data from independent physicians' market survey organization. 2. Scal, J. C.: Eye Ear Nose & Throat Month. 38:738 (Sept.) 1959.

J. B. Roerig and Company
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®
New York, N. Y. 10017

what time is it?

For the past
two years
there's been
one new case
of active tuberculosis
reported for every
four thousand
of U.S. population.

it's time to tine.

Tuberculin, Tine Test

(Rosenthal) Lederle

Available in 5's and 25's.
Order now
from your pharmacist
or your Lederle
representative.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York Lederle

414-6—4046R

Need Is Growing for Health Service Workers

The nation must attract ten thousand recruits a month to the field of health services over the next 10 years.

This critical need for health service workers is emphasized in *Training Health Service Workers: A Critical Challenge,* released recently by Secretary of Labor W. Willard Wirtz and the Secretary of the Department of Health, Education and Welfare, John W. Gardner.

The publication documents a joint Labor-HEW Conference held in Washington, D.C. February 14 to 17, 1966 as part of the President's Job Development Program.

In his greeting to the 300 conference members representing labor, management, government, education and health organizations, President Johnson noted that "One of the basic goals of the Great Society is to guarantee that our people receive the best possible health care." He said that critical manpower shortages in the health services were hindering efforts to insure a healthy America.

Secretary Wirtz called for "auxiliary health manpower" to meet needs in the health fields. He also recommended establishing "job ladders" stepping up wages and opportunities to attract new recruits to these careers.

The Under Secretary of the Department of HEW Wilbur J. Cohen emphasized the importance of making modern medical science and health care readily available to all people.

Refresher courses for inactive professional health workers were considered as one possible method of increasing the number of qualified health workers.

Copies of the publication may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Your public relations problem has been our prime consideration in collection procedures during two generations of ethical service to the Medical Profession.

✶

THE DOCTORS BUSINESS BUREAU

Since 1916

821 MARKET ST., SAN FRANCISCO 94103
GArfield 1-0460

Easy on the Budget...
Easy on the Mother

Tablets & Elixir

For Iron Deficiency Anemia

FAMOUS
Fergon®
brand of FERROUS GLUCONATE

BREON
BREON LABORATORIES INC.
Subsidiary of Sterling Drug Inc.
90 Park Avenue, New York, N.Y. 10016

Milk Drinking and Respiratory Infections

The child who seems to have one cold after another may be reacting to something in his diet.

A Canadian physician reports four cases in which children's severe respiratory infections were relieved when cow's milk and dairy products were removed from their diets.

He is not suggesting that all children with repeated respiratory tract infections are allergic to milk, emphasized John W. Gerrard, M.D., of the Department of Pediatrics, University of Saskatchewan, Saskatoon, Canada. The problem may be more common, however, than is generally realized, he said.

The report appears in the November 7 *Journal of the American Medical Association.*

In each of the four reported cases, one of the child's parents had a similar problem. All improved when they stopped eating dairy products.

In a few cases, the family members who had respiratory trouble actually craved milk. Dr. Gerrard suggested that craved foods may be the ones causing trouble, for these often appear to be the ones to which persons are sensitive.

The four children had markedly different symptoms. One child was flown to a hospital in coma with a diagnosis of congenital heart disease. Another had abdominal swelling; another had persistent anemia.

In all four cases, however, the symptoms disappeared when dairy products were removed from the diet. A variety of other foods were also eliminated from the diets of three of the children. These included soya-bean products, rice, corn oil, oranges, chocolate, and oats.

Dieting Results in an Anti-Coronary Club

A substantial decrease in coronary heart disease is reported among New York men who modified their diet for five years as members of an Anti-Coronary Club.

The report appears in the November 7 *Journal of the American Medical Association.*

The incidence of "coronary events" among 814 volunteers, 40 to 59 years old, was only a third as great as that among a control group of 463 men of the same age.

Significant reductions in obesity and hypertension also were noted among the study group. These conditions remained unchanged in those who did not use the special diet.

The study was designed to test the hypothesis that reducing serum cholesterol in the diet will reduce coronary heart disease. This was done by designing a "prudent diet" that cuts intake of saturated dietary fats. The project has been conducted since 1957 by the Bureau of Nutrition of the New York City Department of Health.

Much further study needs to be done, the investigators point out, because the amount of new heart disease among groups of this size is relatively small. Follow-up studies also are needed on the men who have experienced various kinds of heart malfunctions.

Among men aged 40 to 49 who used the special diet for five years, there was a heart-disease incidence rate of 339 per 100,000 years, compared with 642 per 100,000 among the non-dieters.

In the 50 to 59 age group, the rates were 379 per 100,000 among dieters and 1,331 per 100,000 in the control group.

The men in the study volunteered after learning of the program through newspaper and radio announcements. None had experienced coronary heart disease before the study began. They underwent extensive periodic physical examinations, and followed specially prepared diets.

Some men dropped out of the study before it was completed, but many were contacted later, and health histories were obtained from most of these.

There was great success in reducing obesity among men who participated in the study, the investigators said, and this may have been a contributing factor to the reduction of heart disease.

Cigarette smoking was not a factor, they said, because both groups had similar smoking patterns.

Although much more study is needed, serum cholesterol reduction seems worthy of consideration as a preventive medical program for the community, the authors said.

"The practicing physician can use the serum cholesterol determination to screen his high-risk patients. Armed with knowledge, skill, and time, he can practice preventive medicine in his own

(Continued on Page 44)

Climate
For Growth

Devereux vocational programs...
blending job counseling,
on-the-job training, testing,
job placement aid.

. . . providing comprehensive vocational environments within the Devereux residential treatment programs for mentally retarded and emotionally disturbed children.

DEVEREUX SCHOOLS
UNDER THE DEVEREUX FOUNDATION
A NON PROFIT ORGANIZATION

Helena T. Devereux
Founder and Consultant

Edward L. French, Ph.D.
President and Director

FOR INFORMATION AND LITERATURE
Santa Barbara (Box 1079), California
Keith A. Seaton, Director of Admissions
Devon, Pennsylvania and Rutland, Massachusetts
Charles J. Fowler, Director of Admissions
Devereux Schools, Devon, Penna. 19333
Victoria (Box 2666), Texas
Richard D. Grant, Registrar

Doctor's Wallet

L2-11

Holds money, prescription pad, doctor's cards and his own pen or pencil in a finely crafted imported English Morocco case. BLACK OR BROWN.

$10.00 EACH—2 FOR $18.00

Add 50¢ Postage and Handling
NO C.O.D.

BENTLEY SALES
821 Market Street
San Francisco, Calif. 94103

★

Specialized Service
IN
PROFESSIONAL LIABILITY INSURANCE

is a high mark
of distinction

THE
MEDICAL PROTECTIVE COMPANY
FORT WAYNE, INDIANA
Professional Protection Exclusively since 1899

NORTHERN CALIFORNIA OFFICE:
Gordon C. Jones and John K. Galloway, Representatives
1518 Fifth Avenue, San Rafael, Telephone: 415-453-5140
Mailing Address: P.O. Box 1079, San Rafael 94902
SOUTHERN CALIFORNIA OFFICE:
Davis S. Spencer and Grady T. Dyer, Representatives
Suite 3, 33 East Huntington Drive, Arcadia, Tel. 213-681-5239
Mailing Address: P.O. Box 543, Arcadia 91008

Fortify Nonfat Dry Milk, AMA Urges

(Continued from Page 19)

ards of identity for nonfat dry milk, established by Congress in 1944, do not allow for fortification with vitamins A and D.

"Therefore, it is recommended that appropriate congressional action be taken to amend the Act of Congress of March 2, 1944, which established a standard of identity for nonfat dry milk solids, so that it will allow for the fortification of nonfat milk solids with vitamins A and D."

Typhoid Immunization in U.S. Is Not Recommended

Surgeon General William H. Stewart of the Public Health Service stated that routine typhoid immunization is *not* recommended in the United States. His statement was based on findings of the Public Health Service Advisory Committee on Immunization Practices. Text of the recommendations were released in the Morbidity and Mortality Weekly Report. The Report is published by the Communicable Disease Center in Atlanta. The Committee, composed mostly of experts from without the Service, met recently at CDC.

The Committee recommended selective immunization in the following situations:

1. Intimate exposure to a known typhoid carrier as would occur with continued household contact.
2. Community or institutional outbreaks of typhoid fever.
3. Foreign travel to areas where typhoid fever is endemic.

The Advisory Committee stated further, "Although typhoid vaccine has been suggested for individuals attending summer camps or those in areas where flooding has occurred, there are no data to support the continuation of these practices."

The incidence of typhoid fever in the United States has declined steadily for many years. At the present time, the Committee said, less than 500 cases are reported annually, and a continuing downward trend can be expected. Cases are sporadic and are primarily related to contact with carriers rather than to common source exposure.

Referring to vaccines for paratyphoid A and B, which are typhoid-like fevers, the Advisory Committee stated, "The effectiveness of paratyphoid A vaccine has never been established, and recent field trials have shown that available paratyphoid B vaccines were ineffective. In view of these data and recognizing that paratyphoid A and B antigens when combined with typhoid vaccine may increase the occurrence of vaccine reactions, use of paratyphoid A and B vaccines is *not* recommended."

California
Medicine

Psoriasis in Childhood

EUGENE M. FARBER, M.D., AND RAY A. CARLSEN, M.D., *Palo Alto*

■ *Psoriasis beginning in childhood is more common in girls than in boys, and commonly other members of the patient's family also have the disease. When it begins in childhood, the course of the disease is generally more severe than when it begins in adult life. It is important to avoid therapy or trauma that will aggravate the course of the disease. Care should be taken to fully educate the psoriatic patient and his family.*

PSORIASIS IN CHILDHOOD is not uncommon. Study of the disease in a pediatric age group is important because of psychological problems, dangers inherent in treatment and alteration of the natural course of the disease by injury to the skin. This report of 268 cases of childhood psoriasis is based on observation of patients cared for at the Stanford-Palo Alto Hospital Outpatient Clinics and on information obtained from dermatologists who have cooperated in the psoriasis research program at Stanford. It deals with the natural history of psoriasis in children with respect to incidence, prognosis, and treatment.

Material

Data were gathered from one thousand persons with psoriasis. A comparison was made of psoriasis which begins in childhood with that which has its onset in adult life. The patients in whom psoriasis began at age 15 or earlier will hereafter be referred to as the childhood group, and the remainder as the adult group. There are, of course, many of the childhood group who are now of adult age.

In the comparison between the two groups we have tabulated the sex, familial incidence, the incidence of the Koebner reaction* and the current involvement with psoriasis. The latter was estimated from the percentage involvement of the skin surface on a diagram of the human body provided to the patients and from physical examination by the physician.

Results

Of the one thousand persons whose case records were examined, 268 (27 per cent) reported the onset of psoriasis at or before the age of 15 (Chart 1). The median age of onset was 26.5 years.

There were twice as many girls (180) as boys (88). Analysis of data from 732 patients with psoriasis in whom lesions developed after age 15 revealed an incidence of 48 per cent in males and 52 per cent in females (Table 1).

This work was supported by a grant from The John A. Hartford Foundation.

Presented before the Section on Dermatology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Department of Dermatology, Stanford Medical Center, 300 Pasteur Drive, Palo Alto 94304 (Dr. Farber).

*Refers to the appearance, in psoriatic persons, of a lesion of psoriasis at the site of an injury to the skin.

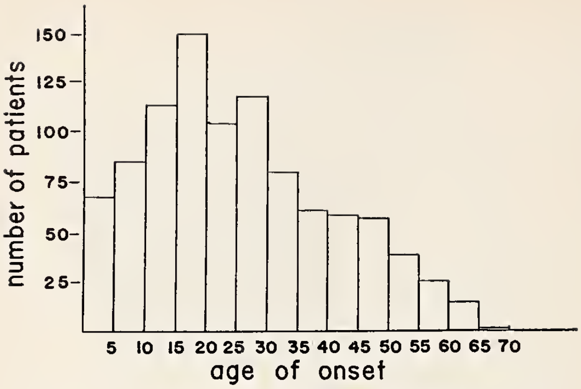


Chart 1.—Age of onset of psoriasis in 1,000 patients.

The familial incidence between the groups differed. Fifty-two per cent of the childhood group named relatives with psoriasis whereas only 30 per cent of the adult group knew of relatives with psoriasis. Parents, specifically, were named in 23 per cent of the childhood group and by 15 per cent of the adult group as having psoriasis.

The Koebner reaction was noted in 106 of the 268 patients who had early onset of psoriasis and in 292 of 732 of the adult group—an incidence of approximately 40 per cent in each group. The patients whose current body involvement with psoriasis was estimated were divided into four groups: 0 to 5 per cent represented *minimal* involvement, greater than 50 per cent represented *widespread* involvement, and there were two intervening groups. As noted in Table 3, there was a much higher proportion of minimal involvement in the adult group than in the childhood group. Table 3 also includes adults who had had psoriasis for at least ten years and was included to account for the possibility that the heavier involvement was a result of the childhood group carrying the disease for a greater number of years. Over half of this group is still minimally involved with psoriasis.

Statistical Analysis

The data in this study were analyzed to determine the significance of the findings. Table 1 and 2 had *chi square* values calculated in excess of 6.64 and were therefore considered significant at the 1 per cent level.

TABLE 1.—*Sex Incidence in Childhood Psoriasis*

	Childhood Group		*Adult Group*	
	No. of Patients	*Per Cent*	*No. of Patients*	*Per Cent*
Male	88	33	353	48
Female	180	67	379	52
Total	268	100	732	100

TABLE 2.—*Familial Incidence in Childhood Psoriasis*

	Childhood Group (268 Patients)		*Adult Group (732 Patients)*	
	Number	*Per Cent*	*Number*	*Per Cent*
Psoriasis in any relative	139	52	219	30
Psoriasis in a parent	62	23	112	15

The figures of the adult group compared with those of the childhood group of Table 3 were significant to the 1 per cent level as determined by the Wilcoxon Rank Test for ordered 2×C contingency tables.[7] The *chi square* for this table was 2.75 and was therefore significant at the 5 per cent level.

The adult group compared with the childhood group in Table 3 by the Wilcoxon Rank Test showed a significance at the 5 per cent level and a *chi square* of 2.08—significant to the 10 per cent level.

Discussion

The preceding tables show a significant proportion of persons with psoriasis beginning at or before age 15, and that females are affected in a ratio of 2:1 over males. These figures are different from those of Lomholt[11] who found that 54 per cent of the patients in his study had onset of psoriasis before the age of 15 years; our data showed an incidence of 26 per cent in the same age group. Lomholt found the incidence almost equal between the sexes. However, his female group had a very prominent peak of onset between the ages of five and nine years. Sixty-two per cent of the females and 45 per cent of the males in his study had lesions of psoriasis before the age of 15. Thirty-two per cent of the females and 20 per cent

TABLE 3.—*Current Body Involvement of Three Groups* of Psoriatic Patients*

Per Cent of Body Covered	*Childhood*		*Adult*		*†Adult (More Than 10 Years)*	
	Number	*Per Cent*	*Number*	*Per Cent*	*Number*	*Per Cent*
0-5	42	38	215	60	140	53
6-15	27	24	78	15	46	17
16-40	27	24	85	17	55	20
More than 50	16	14	36	7	34	9
	112		414		275	

*All patients are over 25 years of age.
†Psoriasis present at least 10 years.

of the males in our study had onset of psoriasis during this period. Other studies support these findings that show early onset proportionally greater in females than in males.[2,13]

There are numerous references in the literature supporting the familial and hereditary patterns of psoriasis.[1,10,11,13,14] Early works also refer to transmission of the disease from parents to children.[8,9,12] The data in the present study also show psoriasis in a considerable proportion of members of the families of patients who have this disease. In this study the childhood group had a higher familial incidence than the adult group.

Patients seem to be more severely involved with psoriasis in adult life if it begins in childhood (Table 3). As the number of patients examined in the study was large, this finding probably is valid. In this regard our findings support Lomholt, who stated that patients in whom psoriasis had begun at less than ten years of age were more subject to periodic major eruptions than were those who did not have onset of disease until after age 25.

Although the data in Table 3 imply that the

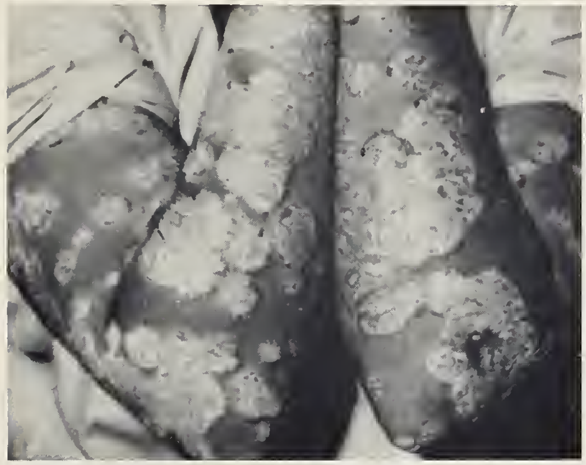


Figure 1.—Widespread disfiguring psoriasis in a 12-year-old.

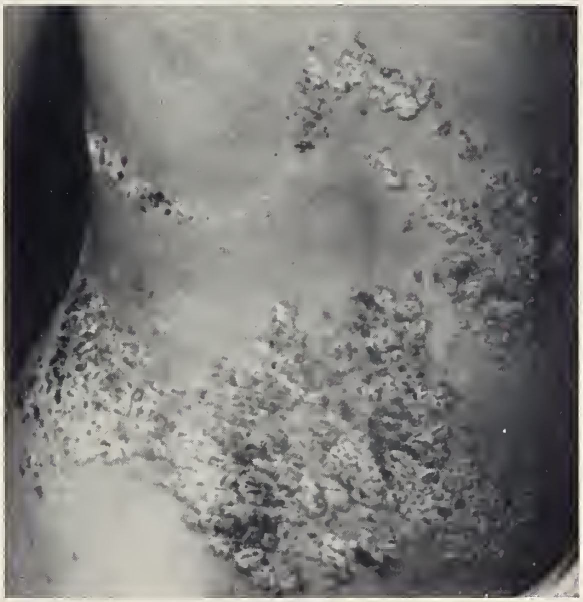


Figure 2.—A six-year-old girl with heavy psoriatic crusts on abdomen and flanks.

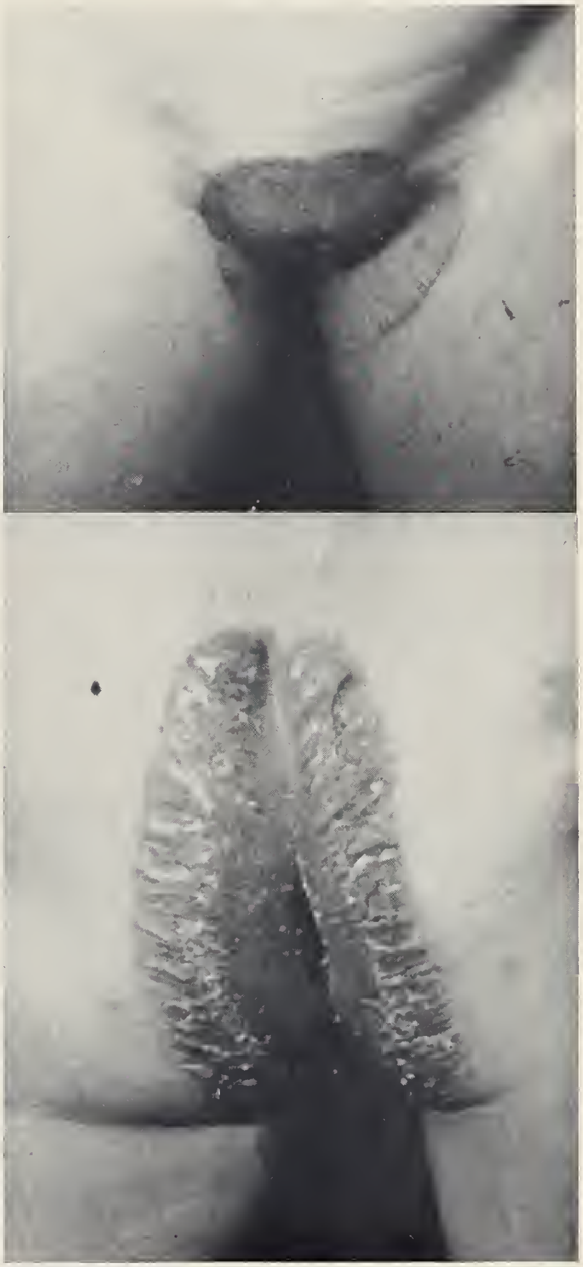


Figure 3.—Severe intertriginous psoriasis in a three-year-old child.

course of psoriasis is worse if the onset is early, it by no means is the rule for all children with psoriasis. We have often seen (and our present report reflects this) cases of early onset which remain relatively quiescent into adulthood. We have also seen one set of identical twins who had quite similar courses, while in another set the courses were widely disparate—mild in one and severe in the other.

As a rule, children do not have the permanent, thick, hyperkeratotic plaques of psoriasis that adults often have on their knees and elbows. More often the lesions are thinner and softer, are nummular and seem less permanent than those of adults. Also generalized erythroderma in childhood psoriasis is rare, as is the pustular form of the disease. Although these last statements imply that childhood skin may react differently to psoriasis than adult skin, our data show that psoriatic lesions do not develop at the site of injury more often in the childhood group than in adults. Our data does not take into account the various types of injury that occurred in both groups of patients, although knowing the kind of injury has been found to be of at least theoretical value.[4,5]

Management

The objectives of treatment are:

- To preserve skin surfaces.
- To afford physical relief from the disease as much as possible with present methods.
- To use measures which do not endanger the health of the child or his future development.
- To educate patient and parents in all aspects of the disease, with proper emphasis on the physical and psychological aspects.

In general the course of psoriasis in childhood is mild and, with infrequent exceptions, can be controlled with conservative therapy. An active program must be undertaken for the preservation of normal skin and for treatment of existing lesions. It is equally important that the parents of the patient completely understand the treatment and the rationale of its use. Certain facts should be brought to their attention: (1) Injury to the skin can result in more psoriasis (Koebner response); (2) psoriasis is a lifelong benign disease subject to natural remission in one-third of all cases; and (3) any therapy that is undertaken should be conservative, deliberate and cognizant of side reactions.

There are various kinds of damage to the skin that give rise to new psoriatic lesions. Bruises, abrasions and scratches all may result in new lesions, and this must be fully understood by the parents. Even rings, elastic undergarments or snug shoes can injure the skin enough to cause a reaction. Excessive exposure to solar rays also result in development of a lesion, although gradual exposure can be beneficial. Some drugs, such as sul-

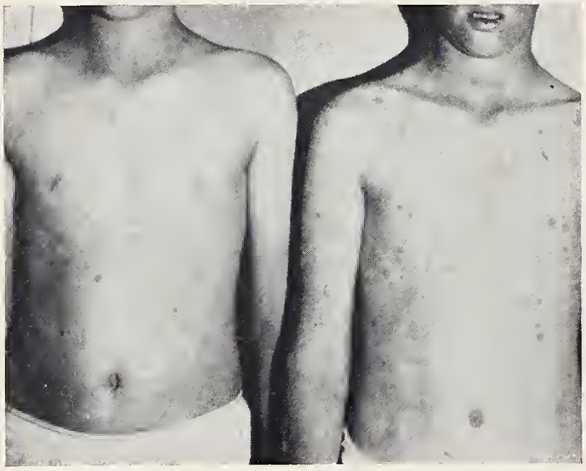


Figure 4.—Guttate psoriasis in identical twins in whom disease had similar course.

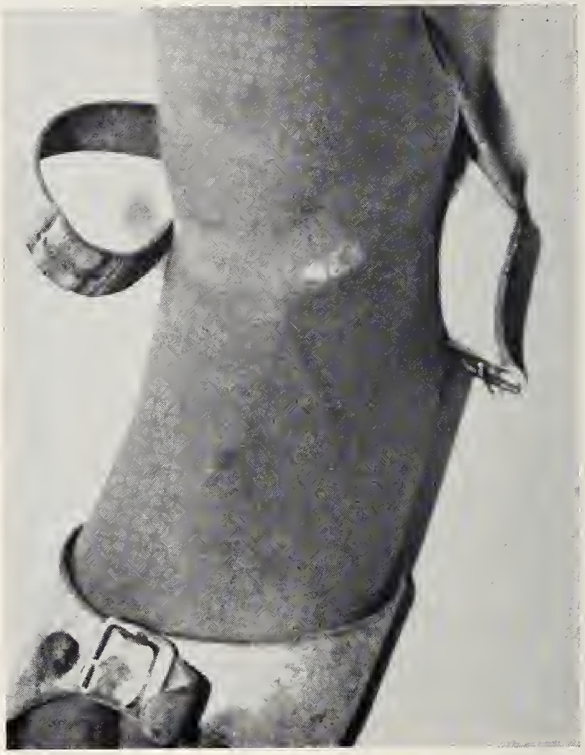


Figure 5.—An example of a new psoriatic lesion after trauma from normal apparel.

phonamides, phenothiazines and declomycin, may produce photosensitivity reactions which result in new lesions of psoriasis.

The approach to medications should be conservative. A burdensome program with unpleasant preparations invites rejection of therapy by the child, whereas a slower beginning with more acceptable medications can bring cooperation. It is important that the child learn day-to-day care, and in this a simple daily routine can be very effective. Soiling of clothes and furniture by messy ointments is a deterrent to conscientious therapy.

Often the lesions of psoriasis will respond to moderate therapy but be resistant to stronger methods. Therapy with ultraviolet light is a good example of simple and natural treatment. After instruction, a child can use an ultraviolet lamp to substitute for hours in the summer sun. Both the child and the parents must be warned of the hazards of overexposure.

Some of the methods of treatment known to be acceptable and effective for adults should not be used for children. Because of the possibility of inducing permanent skin changes, we eschew x-radiation in chronic benign childhood disease. Systemic corticosteroids, used in effective amounts cannot be continued long without interfering with normal growth of a child. Use of them is also accompanied by a generalized spread of psoriasis when the drug is discontinued.[6] Similar problems may occur following the use of topically applied corticosteroids over large areas of skin, although limited use for localized lesions may be helpful. Recalcitrant plaques of psoriasis can often be reduced by applying corticosteroids and then covering the area with plastic wrap (*e.g.* Saran Wrap). This method is for limited areas, and the physician should be aware of possible striae formation.[3]

The use of antimetabolites in the treatment of psoriasis requires care and close supervision of the patient. We do not believe that they should be used in a pediatric age group, except perhaps in extraordinary circumstances.

Psychological Aspects

For children as well as for adults skin disease is repugnant. In adolescence, especially, beauty and handsomeness seem all-important. If psoriasis threatens the self-esteem of a child, it is the duty of the physician to provide necessary emotional support and understanding.

Knowledge of the natural history of psoriasis provides the child with insight sufficient to maintain his self-esteem. And parents who are well informed and free of doubt can ease the concern of their friends and associates.

Widespread visible lesions of psoriasis may cause emotional problems, but once the problems are recognized they can be dealt with by the child and the family under the physician's guidance. Problems of great severity may necessitate psychiatric help or individual schooling. An artificial environment should be avoided if possible, however, and the child should be encouraged to participate in the ordinary activities of his age group. The parents, with the aid of the physician, can help the child make the adjustment to a lifelong problem.

Prognosis

When psoriasis begins in childhood there is reason to believe from our own studies and those of others[11] that it portends increased severity in adult life. This implies profound effects upon the patient's life and his decisions. As the child matures, he not only learns that psoriasis will always be an intimate part of his waking hours, but he also must recognize that there are certain occupations which are incompatible with the state of his skin. Ideally, work and play that inherently traumatize the body should be avoided (construction work, contact sports) but exposure to sunshine and engaging in physical activity should be encouraged. There are no ideal occupations, but some are better than others. A desk worker with psoriasis is probably better off than a carpenter with psoriasis who traumatizes his hands, arms and knees.

Since psoriasis is a lifelong disease, characterized by exacerbations and remissions, it is proper for those contemplating marriage to be fully apprised of the nature of this disease. Because of the familial pattern, marriage between two psoriatic persons should take place only with full awareness of the increased incidence of psoriasis in their offspring.

REFERENCES

1. Aschner, B., Curth, H. O., and Gross, P.: Genetic aspects of psoriasis, Acta Genet., 7:197-204, 1957.

2. Bulkley, L. D.: The cure of psoriasis with a study of 500 cases of the disease, observed in private practice, J.A.M.A., 47:1630-38, 1906.

3. Chernosky, M. E., and Knox, John M.: Atrophic striae after occlusive corticosteroid therapy, Arch. Derm., 90:15-19, January 1964.

4. Eddy, Capt. D. D., and Farber, E. M.: Experi-

mental analyses of the isomorphic (Koebner) response in psoriasis, Arch. Derm., 89:579-588, April 1964.

5. Farber, E. M., and Eddy, D. D.: The natural history of psoriasis, Vol. I, Proc. of the XII Internat. Cong. of Derm., Wash., D. C., September 1962.

6. Farber, E. M., and Peterson, J. B.: Variations in the natural history of psoriasis, Calif. Med., 95:6-11, July 1961.

7. Goldstein, A.: Biostatistics, The Macmillan Co., New York, 1964, pp. 114-117.

8. Hyde, J.: Diseases of the Skin, Henry Lea's Son and Co., 1883, p. 200.

9. Kaposi, M.: Diseases of the Skin, William Wood and Co., New York, 1895, pp. 306-307.

10. Lerner, C.: Hereditary influences in psoriasis, J. Invest. Derm., 3:347-356, 1940.

11. Lumholt, G.: Psoriasis, prevalence, spontaneous course and genetics, G.E.C., Gad, Copenhagen, 1963, pp. 31-36, 43-50, 98-106, 180-183.

12. Nelligan, J. M.: A Practical Treatise on Diseases of the Skin, 2nd Amer. ed., Blanchard and Lea, 1857, p. 178.

13. Steinberg, A. G., Becker, S. W., Jr., Fitzpatrick, T. B., and Kierland, R. R.: A genetic and statistical study of psoriasis, Am. J. Human Genet., 3:267-281, 1951.

14. Ward, J. H., and Stephens, F. E.: Inheritance of psoriasis in a Utah kindred, Arch. Derm., 84:589-596, 1961.

CORRECTION

An error appeared in the article "Protein-Losing Gastroenteropathy" which was printed in the September 1966, issue of CALIFORNIA MEDICINE.

On page 203, the sentence beginning four lines from the bottom of the right hand column should read: Though sodium chromate would tag red blood cells when incubated with whole blood, chromic chloride would effectively label albumin when incubated with plasma.[5]

Paracervical Block in Obstetrics and Gynecology

JAMES E. DAVIS, M.D., *Inglewood*

■ *Paracervical block anesthesia in the practice of obstetrics and gynecology is being used more and more often. It is accepted as a simple, safe and effective method. The author and his associates have used it in their private practice in more than three thousand patients. In almost all cases it completely relieves the pain of the first stage of labor, although additional anesthesia must be given for delivery. It is ideal for dilatation and curettage in poor risk patients and in patients with an incomplete abortion.*

PARACERVICAL BLOCK anesthesia is being used more and more in this country. Numerous enthusiastic reports have appeared in various medical journals. This simple, safe and effective means of relieving pain eliminates the need for depressing amounts of analgesic drugs. No serious maternal or fetal complications have been reported.

The principal use of paracervical block anesthesia is in relieving the pain of the first stage of labor, where the relief it affords is quicker and greater than that produced by drugs which act on the central nervous system.

Neuroanatomy

First stage labor pain is due mainly to dilatation of the cervix and to a lesser degree to uterine contractions.[3] The sensation of pain is due to impulses passing by sensory and sympathetic nerve pathways down the lateral and posterior portions of the cervix into the area of the uterosacral ligaments. The impulses travel through the uterine, pelvic and hypogastric plexuses into the lumbar and lower thoracic chain to the rami of the eleventh and twelfth thoracic nerves to reach the spinal cord. This route has been substantiated clinically by the complete relief of pain afforded when spinal, caudal, epidural, upper lumbar sympathetic, lower thoracic, paravertebral, uterosacral or paracervical block is used.

Pain of the second stage is produced primarily by distension of the lower birth canal, vulva and perineum and is conveyed by sensory pathways of the pudendal nerves, which enter the spinal cord via the posterior roots of the second, third and fourth sacral nerves. Paracervical block, therefore, is not sufficient for delivery.

Procedure

Most anesthesiologists feel that any anesthesia, even a local anesthesia, works more smoothly if premedication is used. This is true with the paracervical block. I use meperidine hydrochloride (Demerol®), promethazine hydrochloride (Phenergan®) and occasionally secobarbital sodium (Seconal®). They are unnecessary after the block.

The Brittain Transvaginal Needle Guide* facilitates injection. This is a stainless steel tube with a ball on one end to prevent injury to maternal

---

Presented before a Joint Meeting of the Sections on Obstetrics and Gynecology and General Practice at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: 211 North Prairie Avenue, Inglewood 90301.

*Brittain Industries, Inc., 463 North Prairie Avenue, Hawthorne, California.

tissues and a funnel on the other end to allow easy access for the 6-inch 20-gauge needle. The needle protrudes from the guide only 7 mm. This eliminates the danger of too deep an injection and reduces the danger of hematoma formation to nil.

The block is performed with the patient in bed under sterile drapes but without surgical preparation. The cervicovaginal fornix is located with the examining finger and the guide is placed at the 5 o'clock and 7 o'clock positions (Figure 1). It is important to sweep the guide away from the cervix in order to get into the posterior lateral fornix. The needle is then inserted through the guide, aspiration is made and the solution injected.

I use chiefly a 1 per cent solution of lidocaine hydrochloride with epinephrine 1:1,000,000. This is prepared by mixing 50 ml plain 1 per cent lidocaine with 5 ml 1 per cent lidocaine with epinephrine 1:100,000. Epinephrine is contraindicated in the presence of diseases such as diabetes, hyperthyroidism, peripheral vascular disease, hypertension, nephritis and cardiac disease. The addition of epinephrine makes the mixture much safer than plain lidocaine hydrochloride and allows a longer duration of effect, but at the expense of uterine inertia in a certain proportion of cases, sometimes requiring use of an oxytocic agent. The usual dosage of anesthetic agent is 8 to 10 ml on each side. The maximum dosage is 50 ml—that is, 500 mg of lidocaine hydrochloride with epinephrine. Only 300 mg is allowed without epinephrine.

If complete anesthesia is not obtained within two or three contractions, 5 ml is repeated on either or both sides. Sometimes there remains an unanesthetized coin area in the lower abdomen on one or both sides. This can be anesthetized by injection of 5 ml at the 10 o'clock or the 2 o'clock position. I keep one guide curved to allow easier introduction to these anterior locations.

Failure is unacceptable. Repeated efforts should be made until the desired effect is achieved, but with care to stay within the limits of safe dosage. It must be emphasized that the greatest danger is overdosage.

The block is given in the accelerated phase of labor, usually at about 5 cm cervical dilatation. Using lidocaine hydrochloride with epinephrine, the duration of anesthesia is approximately one hour and twenty minutes.

The quality of uterine contractions after the block might seem poor and yet the progress in cervical dilatation be dramatic. This is because the cervix has become so soft and free of tone that even the mild contractions lead rapidly to complete dilatation. Because of atonicity, cervical lacerations are rare.

We have done over four thousand blocks using this material in private practice. There have been no serious maternal complications. An occasional patient has complained of feeling faint or apprehensive from too rapid absorption, but these complaints have been very transient. Temporary numbness of one or both legs noted by some patients, disappears as the paracervical anesthesia abates. There have been no instances of hematoma, thrombosis, infection, hypersensitivity reaction or lumbosacral plexus neuritis. The only untoward effect is fetal bradycardia, noted in 4.7 per cent of cases. This should not be viewed with alarm; it is probably due to a vasovagal reflex, and must be distinguished from fetal distress.

Infants have been delivered during the period of bradycardia in some cases and after its disappearance in others, and in none of them has fetal

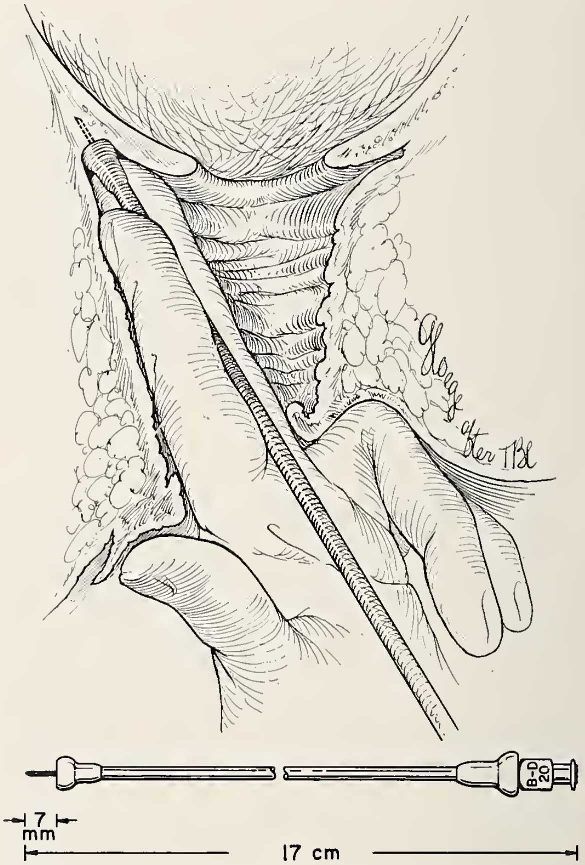


Figure 1.—Administration of paracervical block.

depression been present. On the contrary, the infants are breathing and crying before the delivery is completed. The important point, therefore, is that a careful evaluation must be made to distinguish the cases of fetal bradycardia due to fetal distress from the transient bradycardia observed following paracervical anesthesia.

Gynecologic Use

Paracervical block for anesthesia for curettage is carried out without the Brittain Guide. A 3- or 4-inch 21-gauge needle is adequate, and 5 ml of the anesthetic solution is infiltrated at the 4 o'clock position, 5 ml at 8 o'clock and 5 ml directly into each uterosacral ligament.

This provides the ideal anesthetic for completion of abortions and it is excellent for curettage in many other circumstances. The method is not recommended in the presence of vaginismus of any cause. It is indicated where general anesthesia or sophisticated forms of conduction anesthesia are either unavailable or contraindicated. It is especially useful if the patient has anemia, has too recently eaten or has a respiratory problem or is in borderline shock. Many patients with incomplete abortions fall into this category.

Paracervical block can also be used in other minor procedures such as cervical repair, conization and Shirodkar or Wurm operations, although in such cases it is probably better to reserve it for the exceptionally poor risk patients.

Paracervical block has also been recommended as an aid in the differential diagnosis of dysmenorrhea. If the block does not relieve the pain, no benefit can be expected from the Doyle procedure of dividing the uterosacral ligaments or from a presacral neurectomy. As I am not enthusiastic about the surgical approach to dysmenorrhea, I would find this a rather rare use.

GENERIC AND TRADE NAMES OF DRUGS

Meperidine hydrochloride—*Demerol Hydrochloride.*
Promethazine hydrochloride—*Phenergan.*
Secobarbital sodium—*Seconal Sodium.*
Lidocaine hydrochloride—*Xylocaine Hydrochloride.*
Propitocaine—*Citanest.*

REFERENCES

1. Aldridge, C. W., Jr., Nanzig, R. P., and Beaton, J. H.: Uterosacral block and the obstetrical anesthesia problem, Amer. J. Obstet. Gynec., 81:941, 1961.

2. Baken, M. D., Jr., Freeman, D. W., and Barno, A.: Transvaginal regional block anesthesia in labor, Gur. Gynec. Obstet., 114:375, 1962.

3. Bonica, J. J.: What's New, No. 217, Abbott Laboratories, North Chicago, Spring 1960.

4. Davis, J. E., Frudenfeld, J. C., Frudenfeld, K., and Webb, A. N.: Paracervical block for pain relief in labor, Obstet. Gynec., 19:195, 1962.

5. Davis, J. E., Frudenfeld, J. C., Frudenfeld, K., Frudenfeld, J. H., and Webb, A. N.: The combined paracervical-pudendal block anesthesia for labor and delivery, Amer. J. Obstet. Gynec., 89:366, 1964.

6. Davis, J. E., and Frudenfeld, K.: Improved transvaginal needle guide, Obstet. Gynec., 23:143, 1964.

7. Freeman, D. W., Bellville, T. P., and Barno, A.: Paracervical block anesthesia in labor, Obstet. Gynec., 8:270, 1956.

8. Kobak, A. J., Sadove, M. S., and Mazeros, W. T.: Anatomic studies of transvaginal regional anesthesia, Obstet. Gynec., 19:302, 1962.

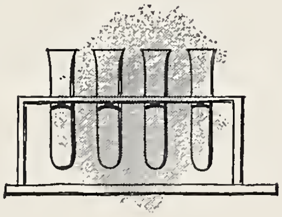
9. Page, E. P., Kamm, M. L., and Chappell, C. C.: Usefulness of paracervical block in obstetrics, Am. J. Obstet. & Gynec., 81:1094, 1961

10. Seeds, A. E., Jr., Stein-Messanger, P., and Dorsey, J. H.: Paracervical blocks: Results of a double-blind evaluation, Obstet. Gynec., 20:462, 1962.

11. Seley, J. E., and Gold, E. M.: Paracervical block in the management of labor, Obstet. Gynec., 27:116, 1966.

12. Van Praagh, Ian, G. L., and Povey, W. G.: Paracervical block anesthesia in labour, Canadian Med. Assn. J., 94:262, 1966.

13. White, C. A., and Pitkin, R. M.: Paracervical block anesthesia in obstetrics, Post grad. Med., 33:585, 1963.



Long Acting Single Injection Caudal Anesthesia

1,208 Obstetrical Deliveries with Mepivacaine

RONALD E. GUNTHER, M.D., *Palo Alto*, AND
W. BENSON HARER, JR., M.D., *Rialto*

■ *Long acting, single injection caudal anesthesia with mepivacaine was studied in 1,208 obstetrical cases.*

A 1 per cent solution was used in 671 patients and compared with a 1.5 per cent concentration in 537. No remarkable differences were found between the two groups. The 1 per cent solution provided relief of labor discomfort for from 60 to 180 minutes with an average of 110 minutes. In contrast, the 1.5 per cent solution provided an average of 115 minutes with a range of 80 to 210 minutes.

A total volume of 30 ml of anesthetic agent yielded anesthesia to a level of the tenth thoracic vertebra or higher in 91 per cent of patients.

Significant alterations in blood pressure were uncommon. About 1 per cent of patients required a vasopressor because of a drop in systolic blood pressure below 80 mm of mercury. Another 8 per cent had a drop of over 20 points in systolic pressure but from high enough levels that they did not require a vasopressor.

Toxic effects similar to those of lidocaine were found in slightly more than 1 per cent of cases.

This anesthesia requires a higher incidence of operative intervention for delivery.

LONG ACTING single injection caudal anesthesia utilizing mepivacaine* was studied in 1,208 obstetrical cases at the 2796th USAF Hospital. Two concentrations were compared. A 1 per cent solution was used in 671 patients and a 1.5 per cent solution for the remaining 537. The safety and efficacy of the drug have been demonstrated in all varieties of forceps deliveries, obstetrical manipulations, immediate postpartum tubal ligations and emergency cesarean sections. The broad applicability of this technique is confirmed by its use in 87.5 per cent of the 1,381 total number of deliveries during the study.

Mepivacaine is a highly stable amide, chemically related to lidocaine and with similar toxicity. However, it has the advantage of longer duration of action. It can be autoclaved repeatedly and stored indefinitely. Its most remarkable characteristic is that little apparent vasodilatation occurs with its use; hence significant cardiovascular changes are rarely experienced.[1,2,3,6]

Technique

The following technique is consistently employed regardless of the patient's height, weight or obstetrical situation. Whenever possible the anesthetic is administered early in the acceleration phase of labor. With the patient in the left lateral

---

From the Department of Obstetrics and Gynecology, 2796th USAF Hospital, Norton AFB.

The contents of this article reflect the personal views of the authors and do not constitute statement of Air Force policy or Air Force endorsement of any commercial product.

Submitted 30 June 1966.

Reprint requests to: Department of Obstetrics and Gynecology, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304 (Dr. Gunther).

*As Carbocaine,® supplied in part by Winthrop Laboratories, New York.

recumbent position, with the right hip and knee flexed, the sacral area is prepared and draped. In the average case we prefer to use a No. 19 two-inch-long malleable Hingson-Edwards needle. A longer needle may be necessary for extremely obese patients, whereas in thin patients with good landmarks an ordinary No. 21 hypodermic needle may be used. The needle is inserted 2 to 3 cm through the sacral hiatus and then connected through approximately 20 cm of rubber tubing to a syringe. This flexible system provides adequate stabilization of the needle with minimum risk of entering the dura. In only two instances during this study was the dura punctured. In both cases, from the free flow of spinal fluid it was felt that the dura came low down in the caudal canal in an anomalous fashion. Accordingly, no anesthetic agent was injected.

Proper placement of the needle is suggested by free injection of 5 to 10 ml of air while the anesthetist's hand palpates over the lumbosacral area to confirm absence of crepitus. A 5 ml test dose of mepivacaine in Ringer's solution is then injected. After elapse of two or three minutes rectal examination is done to demonstrate sphincter relaxation and to palpate the ventral surface of the sacrum and coccyx. This helps to confirm proper placement of the needle and also prevents the unfortunate complication of injecting the anesthetic solution into the fetus. Assuming no associated signs of spinal anesthesia appear within four minutes of observation, an additional 25 ml of anesthetic solution is then given, with aspiration several times during injection to assure against inadvertent spinal or vascular administration. By avoiding scraping the needle against the bone and inserting only a short distance, vascular absorption may be reduced. We deprecate the practice of deliberately scraping along the canal in order to induce bleeding as evidence of proper placement. A sensation of pressure in either or both buttocks, with radiation down the posterior aspect of the leg (sciatic sign), was noted by 80 per cent of the subjects. This sensation is an excellent indication that the injection is in the caudal canal. Because vasodilatation is not pronounced the "warm foot sign" is not as apparent as it is in caudal anesthesia when metycaine or lidocaine is used.

Immediately after injection the needle is withdrawn and the patient placed supine to promote an even level of anesthesia bilaterally. Blood pressure is monitored carefully for the next 30 minutes. In most cases discomfort is relieved within five to 10 minutes, but the maximum level of cutaneous analgesia may not be attained for at least 15 minutes. After the 30-minute observation period, the patient may be observed as to vital signs just as any other patient in labor, since any significant change resulting from anesthesia will occur within this time.[4,5] This does not mean the attendants are relieved of the burden of judicious observation of the patient's progress, but simply that significant alteration in vital signs after this time must be accounted for by other factors.

Duration

Because of its long duration, a single injection provided adequate anesthesia for the remainder of labor and delivery in 91 per cent of the patients in the study. The remaining 104 patients received from two to four injections each by repeat puncture, in order to suitably prolong anesthesia through delivery. In the group for which 1 per cent mepivacaine was used, there were 55 patients requiring 71 such injections. The duration of anesthesia until it was necessary to repeat it ranged from 60 to 180 minutes, and both the mean and the median duration was 110 minutes. In contrast, 49 of the patients given 1.5 per cent mepivacaine required a second injection to carry them through labor to delivery. In this group the duration of the first injection ranged from 80 to 210 minutes with a mean time of 115 minutes and a median of 110 minutes. Because there is so little difference between the two groups, we prefer the 1 per cent concentration for routine use, since theoretically the risk of toxic reaction is less. With either concentration perineal anesthesia generally persisted about 45 minutes longer than anesthesia at the high level necessary for relief of uterine contractions, thus providing ample time for repair of episiotomy or lacerations. The longest total duration of anesthesia was 8 hours and 15 minutes in a primagravida who received four such injections of 1 per cent mepivacaine.

Level of Anesthesia

All data were analyzed separately according to the strength of anesthetic solution. However, where no significant differences were found the two groups were combined for simplicity of presentation.

The level of anesthesia is primarily dependent upon the volume of anesthetic solution injected rather than its concentration. The patient's height, weight and gross skeletal structure did not correlate well with the level of anesthesia attained using the standard 30 ml dose. The 30 ml injection provided anesthesia to the level of the tenth thoracic vertebra or higher in 91 per cent of cases. A level below this was generally inadequate to relieve labor pains completely; hence, when circumstances permitted, a supplementary injection was given by repeat puncture to raise the level. The ideal level —from the tenth to the eighth thoracic vertebra— was achieved in 77 per cent, while a level from the second to the fourth occurred in only 2.5 per cent. A high level did not cause any particular problems.

Circulatory Changes

Significant alterations in blood pressure were quite uncommon (Table 1), with little difference between the 1 per cent and the 1.5 per cent series. A vasopressor agent was required in only 1.5 per cent of the patients in whom the 1 per cent mepivacaine solution was used and in only 0.6 per cent of patients given the 1.5 per cent solution. This paradoxical finding occurred because most cases in the 1 per cent group were fairly early in the study, before we became alert to the increased tendency for patients in labor to demonstrate the supine hypotensive syndrome after caudal anesthesia. Probably several of those patients would have responded to turning on the side and would not have required a vasopressor agent.

In the 107 patients of both series who had a blood pressure drop of over 20 mm of mercury, the systolic pressure remained over 80 and the average lowest systolic pressure was 94 mm of mercury. Many of these patients started with blood pressure somewhat elevated from their normal ranges because of the anxiety and pain of labor. In such cases, the fall in pressure cannot be attributed entirely to a hypotensive affect of the drug or to sympathetic block. As our awareness of the supine hypotensive syndrome increased, we found that more and more of the blood pressure drops could be counteracted by the simple expedient of turning the patient to the side, increasing venous return to the heart. Among the other patients with pronounced drop in blood pressure the intravenous administration of 3 to 5 mg of methoxamine resulted in prompt return to normal levels. In only one patient did the blood pressure fall abruptly to a level at which it could not be determined. This occurred five minutes after the usual dose of 1 per cent mepivacaine. The patient responded immediately to methoxamine with no adverse effect either to her or to the fetus.

One other bizarre response was found in a patient given 30 ml of 1 per cent mepivacaine, plus a supplement of 20 ml to raise the level of anesthesia from the twelfth to the seventh thoracic vertebra. Shortly thereafter, her blood pressure dropped to 70/40 mm of mercury associated with bradycardia, 40 beats per minute. The hypotension responded promptly to administration of methoxamine but the bradycardia persisted for approximately 15 minutes before spontaneously returning to the patient's normal rate of 72.

Toxicity

Overdosage or faulty administration resulting in a high blood level of mepivacaine will produce toxic effects similar to those of lidocaine. In this series 15 patients showed evidence of intravenous absorption manifested by a subjective sensation of anxiety and a feeling of impending disaster followed by varying degrees of tinnitus. In all cases this lasted only a few minutes and resolved without treatment. One patient became disoriented and showed athetoid movements of the arms for about one minute, but also had resolution of the symptoms without treatment. There were no instances of unconsciousness, convulsions or precipitous change in vital signs in these patients.

No instances of infection or local tissue reaction were observed in this series. Allergic reactions were not found. No instances of fetal distress or of maternal or fetal morbidity could be attributed to this anesthesia.

Method of Delivery

Provided labor is well established, there is no

TABLE 1.—*Blood Pressure Changes in Patients Given Mepivacaine Solution for Caudal Anesthesia*

Systolic Blood Pressure (mm of mercury)	*Strength of Solution*			
	1 Per Cent Mepivacaine		*1.5 Per Cent Mepivacaine*	
	No.	*Per Cent*	*No.*	*Per Cent*
Over 10 rise	16	2.4	17	3.1
10 ±	452	67.4	343	64.0
10-20 fall	131	19.4	123	23.0
20 fall, systolic remaining over 80	60	9.0	47	8.6
Vasopressor, systolic under 80	10	1.5	3	0.6
No vasopressor, systolic under 80	2	0.3	4	0.7
Total	671	100.0	537	100.0

apparent tendency for early administration of this anesthesia to retard its progress; on the contrary, it is the authors' impression that it speeded and enhanced progress. As would be expected, duration of labor was somewhat longer in primagravidas, and the caudal agent was administered to them somewhat later in labor than in multigravidas. Obstetricians using caudal anesthesia can generally expect to resort more often to operative interference in order to effect delivery. This results from blocking the reflex to bear down in the second stage when the fetal head reaches the pelvic floor. Furthermore, the decided perineal relaxation tends to inhibit spontaneous rotation of the head to the occiput anterior position. With the level of anesthesia in the range of the tenth to the eighth thoracic vertebra, there will usually be sufficient strength in the abdominal musculature to permit cooperative patients to bear down with contractions to promote spontaneous delivery. Many obstetricians, however, would share the author's preference for the use of forceps for delivery. The high incidence of mid-forceps delivery (Table 2) reflects the need for rotation, usually at a low level in the pelvis. We did not feel there was any increased loss of blood associated with this anesthesia.

Contraindications

We feel that the only major contraindications are infection at the injection site or the patient's refusal. The authors believe this technique can be successfully applied in almost any obstetrical situation. Monstrous obesity presents only a minor problem to experienced operators; caudal anesthesia was successfully given to a number of patients in this series whose weight exceeded their ideal by over 150 pounds. There were only eight instances during the study period when the authors were unable to properly place the caudal needle and these were primarily in situations where time did not permit more than one attempt.

It was desired to maintain a simple yet effective regimen of analgesia for the patients in this study. Labor was induced in 39 per cent, all of whom were given 100 mg of secobarbital orally about two hours before starting the induction. Early in labor meperidine (Demerol®) from 50 to 100 mg was given intravenously to 88 per cent of the primigravidas and 50 per cent of the multiparas. We were usually successful in gauging the administration of the narcotic to be one to two hours before administering the caudal injection, and the effects of these medications were well established by the time the caudal injection was made. Thus, confusion as to what changes were produced by the anesthesia and what by premedication was avoided. This proved valuable in providing relaxation and cooperation at the time of administering the caudal while providing ample time during the remainder of labor for the narcotic to be metabolized. As a result evidence of fetal respiratory depression was extremely rare.

Nausea was experienced by 12 per cent of the patients and 7 per cent vomited. There was no significant correlation between vomiting and the total dose or concentration of mepivacaine used. Because of the frequent occurrence of nausea and vomiting in labor it is doubtful that the incidence reported here should be regarded as a significant effect of the anesthesia.

Evaluation of Anesthesia

Besides our preoccupation with the broad spectrum of pharmacologic effects in anesthesia, we must keep in mind that the basic reason for its administration is the relief of pain. In this respect caudal anesthesia appears to be unexcelled in obstetrics. In the present series the physician rated the anesthesia excellent in 1,180 cases or 97.7 per cent (Table 3). In these patients there was complete relief of the discomfort of labor as well as complete routine manual extraction of the placenta and perineal repairs. In 19 cases it was rated only good by the physician, largely because of a low initial level or falling level of anesthesia at the time of delivery. In nine cases it was rated only fair, usually because of a very low or unilateral level. Four of these patients showed a spotty pattern of anesthesia which could not be eliminated by supplementary injection; and in these cases there was a decided flow of blood when the caudal needle was inserted. It is postulated that there may

TABLE 2.—*Method of Delivery*

	Primagravida		*Multigravida*	
	No.	*Per Cent*	*No.*	*Per Cent*
Spontaneous	46	11.0	384	48.2
Low	236	55.6	275	34.5
Mid	124	29.2	110	13.8
Breech	12	2.8	17	2.1
Version	2	0.5	8	1.0
Cesarean	4	0.9	3	0.4
Total	424	100.0	797	100.0

*Includes 13 sets of twins.

have been blood clotting in the caudal canal, preventing the usual effect of the anesthetic agent.

For the most part the patients were also pleased by this anesthesia, 94 per cent rating it excellent. It was considered only "good" by 3.7 per cent even though they appeared to have complete relief of pain. Because of some persisting discomfort associated with a low or falling dermatomic level, it was rated only fair by 1.5 per cent. Only ten patients or 0.8 per cent actually disliked it. Their aversion appeared to be related more to their emotional response to pregnancy and delivery than to adequacy of anesthesia. These patients generally wanted to be asleep.

Advantages

We feel that for general use in obstetrics, the regimen reported herein has specific advantages over other forms of anesthesia, over other techniques for administering caudal anesthesia and over other drugs used in caudal anesthesia. The specific advantages of mepivacaine are long duration and low toxicity.

With this drug the simple single injection technique can match the relief provided by the continuous technique in the vast majority of patients without the inconvenience or adverse psychological effect of having a catheter or needle left in place throughout delivery. In those cases of inadvertent total spinal anesthesia of which the authors have direct knowledge, all occurred upon subsequent injections when a continuous technique was used. When a catheter or needle is left in a patient, there is a risk of dural penetration when she moves. If the patient is left in a lateral recumbent position, unequal levels of anesthesia are commonly found. If the patient in labor is placed in the supine position with a catheter or needle in situ, contamination with rectal contents is almost unavoidable, particularly with patients in labor who have been given an enema.

TABLE 3.—*Physicians' and Patients' Evaluation of Caudal Anesthesia with Mepivacaine*

	Number	*Per Cent*
Physician Opinion		
Excellent	1,180	97.7
Good	19	1.6
Fair	9	0.7
Total	1,208	100.0
Patient Opinion		
Excellent	1,136	94.0
Good	44	3.7
Fair	18	1.5
Disliked	10	0.8
Total	1,208	100.0

Finally, we must consider the advantage over other varieties of anesthesia. The inherent dangers of fetal depression and possible accident to the mother associated with general anesthesia are so well known that the superiority of regional anesthesia of any type need not be extolled. We prefer caudal anesthesia over the currently popular combination of paracervical and pudendal blocks because a more extensive area is anesthetized for a significantly longer time with a significantly smaller amount of anesthetic agent. There seems to be much less risk of technical error or of excessive vascular absorption with a single caudal injection than there would be from multiple injections into vascular areas as with paracervical and pudendal blocks. In comparison with saddle block, which is simple and effective, caudal anesthesia has the great advantage that it can be administered far earlier in labor. As a result the patient can be effectively relieved of pain throughout the most difficult part of labor and delivery with minimum use of narcotics. In addition, with caudal anesthesia the physician can work at a relatively leisurely pace, much more at his convenience, and have a more alert and cooperative patient.

Conclusions

Caudal anesthesia with mepivacaine for obstetrics proved safe and effective in this series. A 1 per cent concentration in Ringer's solution is preferred for routine use, as a 1.5 per cent concentration provides little increase in duration with greater theoretical risk of toxic reaction from increased milligram dosage.

GENERIC AND TRADE NAMES OF DRUGS

Mepivacaine—*Carbocaine.*
Meperidine—*Demerol.*

REFERENCES

1. Dhuner, K. G., Oljelung, O., and Aagesen, G.: Carbocain-d, 1-N-methylpepecolic acid 2,6-dimethyl-anilide. A new local anesthetic agent, Acta Chir. Scandinav., 112: 350, May 1957.
2. Gordon, R. C., Kerr, J. H., and Taylor, R.: A laboratory and clinical evaluation of mepivacaine (Carbocaine®), Can. Anaes. Soc. J., 7:290, July 1960.
3. Griesser, G.: Uber ein neues lokalanaeshtetikum (Scandicain). Dtsch. Med. Wschr., 82:2071, 6 December 1957.
4. Gunther, R. E., and Harer, W. B., Jr.: Single injection caudal anesthesia, Am. J. Obst. & Gynec., 92:305, 1 June 1965.
5. Harer, W. B., Jr., Gunther, R. E., and Stubblefield, C. T.: Long-acting single injection caudal anesthesia, Am. J. Obst. & Gynec., 87:236, 15 September 1963.
6. Wieschel, K. L.: Caudal block with 0.5 per cent Carbocaine® plus Adrenalin, Acta Chir. Scandinav., 119: 72, May 1960.

Phenylketonuria—The Guthrie Screening Test

A Method of Quantitation, Observations on Reliability and Suggestions for Improvement

CHARLES M. BLUMENFELD, PH.D., M.D., MARY JEAN WALLACE, A.B., AND RAMONA ANDERSON, B.S., *Sacramento*

■ *The Guthrie bacterial inhibition assay method of screening neonatal infants for phenylketonuria (PKU) initiated mass screening for inborn errors of metabolism. It is a simple, cheap procedure admirably suited to private local use as against private or public central use. However, using parallel fluorometric determinations as a basis for comparison, and 4 mg per 100 ml serum phenylalanine as a presumptive positive threshhold, the Guthrie test yielded 53 per cent "false negatives." Extrapolating from a combination of our data and reported phenylalanine levels at three days of age or less in proved PKU patients, it is estimated the Guthrie test might fail to detect one of 25 PKU patients screened at three days of age or less. Means to diminish this risk are considered.*

MASS SCREENING for the inborn metabolic error phenylketonuria, justified because the serious consequences of the condition can be greatly diminished upon early detection, was initiated by Guthrie,[3-5] who used a bacterial inhibition assay test. The subsequent development of a more specific, quantitative fluorometric method[2,10] for confirmation of screening results, and for proper control of phenylketonuric patients under treatment, was followed by adaptation of it to automated apparatus for use as a screening test.[7] Anyone who will take the trouble to perform screening studies in parallel by two methods, the GBIA (Guthrie Bacterial Inhibition Assay test) and MRF-AP (McCaman, Robins Fluorometric test, Automated Paper) will quickly confirm the substantial superiority of the latter. Why not, then, with recognition and tribute to its pioneering importance, shelve the GBIA method for good? We offer these considerations in trying to reach a decision:

- Since approximately 10,000 persons must be screened to detect one with PKU, the method employed should be the most reliable and the cheapest.
- A screening method may be quantitatively crude; as long as it always detects significant elevations of phenylalanine, it is reliable.
- Low cost per test can be achieved through volume testing. We believe it is of far-reaching importance that testing be done privately (and, in passing, we salute our Public Health Department for having the same belief). We believe also that

---

From the Department of Pathology, Sutter Community Hospitals, Memorial Division, Sacramento.

Presented before the Section on Pathology at the 95th Annual Session of the California Medical Association, Los Angeles, 19 to 23 March 1966.

Reprint requests to: Sutter Community Hospitals, 52nd and F Streets, Sacramento 95819 (Blumenfeld).

local testing is preferable to centralized testing, public or private, provided it can be done as reliably and as cheaply.

- Provided it is reliable, the GBIA screening test, simple to do and read, is foremost as the method for small volume, local, private performance.

The arguments lead to a single critical question: Is the GBIA test reliable? Employed properly, can the GBIA test be depended on always to detect blood phenylalanine concentrations at that level we consider critical, whether it be 4 mg or 6 mg per 100 ml, or whatever we choose? Considering the minute fraction of positives and the crucial importance of initiating treatment as early as possible, the GBIA test must be 100 per cent reliable.

There has been some question raised about the reliability of the GBIA test as a method for screening for PKU in infants at an early age.[9,12] Irwin[9] reported that of 30 patients with serum phenylalanine levels of 4.1 mg per 100 ml and higher, only 11 had elevated values by the Guthrie method. In his series there were five patients with levels over 6.5 mg, and in four of these the Guthrie test also showed elevation. A recent extensive discussion of this matter by Partington and Sinnott[11] included brief consideration of "false negative" results. In their extensive studies, in which they quantitated zones of growth by measuring the diameter of the bacterial colonies they encountered no such instances.

"False positives" could contribute a serious problem if they were frequent but the incidence is not sufficiently great to make this important. We are concerned with the possible occurrence of "false negatives." Undocumented remarks at a PKU conference[1] in 1965 planted a seed of doubt. We realized we were totally dependent on the reliability of standards commercially available, that at times they appeared to behave differently in successive runs, that two different standards (for example, 4 mg and 6 mg) sometimes looked alike—in short, that we had no quality control.

Consequently we began a series of studies to determine the reliability of the GBIA method, and, if there was room for improvement, to bring it about in such a manner and with such devices as would neither appreciably diminish its simplicity nor increase its cost. Such efforts are continuing; this is an interim report based on results accruing from modifying the medium, quantitating the growth and utilizing data derived from studies not primarily intended for this purpose.

Materials and Methods

Densitometer

We realized we could not critically evaluate performance of the several standards in a given run, compare performance of successive runs or assess the usefulness of modifications of the medium unless we had some way of measuring bacterial growth. Scheel and Berry[12] and Partington and Sinnott[11] quantitated Guthrie tests by measuring the diameter of the zone of growth in millimeters. Close inspection of plates led us to conclude that whereas at times the margins of colonies appeared sharp, there were other times when they were indistinct; hence such measurements could be misleading.

To achieve quantitation at the lowest possible cost, we constructed a densitometer utilizing two selenium photocells (International Rectifier, No. B2M) in a series-aiding circuit. The reference and the reading cells are activated by readily available microscope illumination lamps (GE No. 1493). Utilizing a microammeter with zero at midscale (Triplett Model 320M) the circuits are balanced at zero by positioning the reference photocell in relation to its lamp with a screw drive. The circuit is next switched to a second microammeter with zero at the left end of the scale (Triplett Model 327PL). Polarity connections of the photocells are made so that anything placed in the path of the reading cell causes a deflection to the right, and its density is read in microamperes. To insure full use of the scale (and deflection can be altered by varying lamp intensity) a neutral density filter (Wratten 0.50 density, 32 per cent transmittance) determined by trial to be equal to the effects of bacterial growth around a disk soaked with blood containing 40 mg of phenylalanine per 100 ml is inserted into the reading cell path. Then the current supply is adjusted to give a reading of 40 microamperes.

Means to obtain a reasonably constant lamp current supply is the costliest part of the device. We have tried two combinations: A combination of 30-watt voltage stabilizer (Raytheon RVA-30S), a variable transformer (GE Variable Transformer 9H30AA10X) and a stepdown transformer (Chicago Standards Filament Transformer P-6456) to yield 6.3 volts alternating current; and a nickel cadmium battery pack (Edmund Scientific Co., No. 70,777) with attached charger to supply 7.2 volts direct current, regulated by a variable resistor (International Resistor Co., 2 ohm, 50 watt). With cost a primary consideration, we prefer the latter.

With this apparatus we measured the optical density of bacterial growth around various standards. The deflections recorded are a product of medium, disk and bacterial growth. As the blood-soaked disks are opaque at the light intensity used, they produce a constant effect. The medium and the bacterial growth are the two variables. Readings on unaltered media show variations from zone to zone, usually minor but definite. Were it possible to read the medium all around a disk, plus the growth, a growth density value closest to actuality would be obtained. This has not been possible to now but it is being achieved in a new form of culture container and densitometer under development. In our initial studies we determined the lowest medium density reading and used it as a base line for each plate.

Modified Medium

After experimenting with several substances as a medium, we employed 2,3,5 triphenyl tetrazolium, using 0.05 ml of a 1 per cent aqueous solution added to 50 ml of melted medium (Difco) at a temperature of approximately 55°C. This slowed rate of growth temporarily with interesting effects if plates were read after 20 hours instead of 16 hours of incubation as is done with the regular medium.

Results

Comparative Behavior of Standards on Regular and Tetrazolium Media

The results are given in Table 1 and are presented as graphs in Chart 1. On regular media, readings at 20 hours as compared with 16 showed less variation, but the spread between lowest and highest standards was no greater. On tetrazolium medium, read at 20 hours, the spread was considerably greater, not at the four lower concentrations (2, 4, 6 and 8 mg per 100 ml) but because of results with 12 and 20 mg per 100 ml standards, probably due to the red of the reduced tetrazolium-formazan. Variability was reduced, again only at the 12 and 20 mg per 100 ml concentration standards. The data as plotted can serve as a quality control chart.

The reddish-pink growth on tetrazolium as compared with the grey growth on regular media is possibly slightly easier to evaluate by visual inspection, but the difference is not great. Persons interested should determine for themselves whether or not it justifies one additional step in preparing the medium and reading at 20 instead of 16 hours.

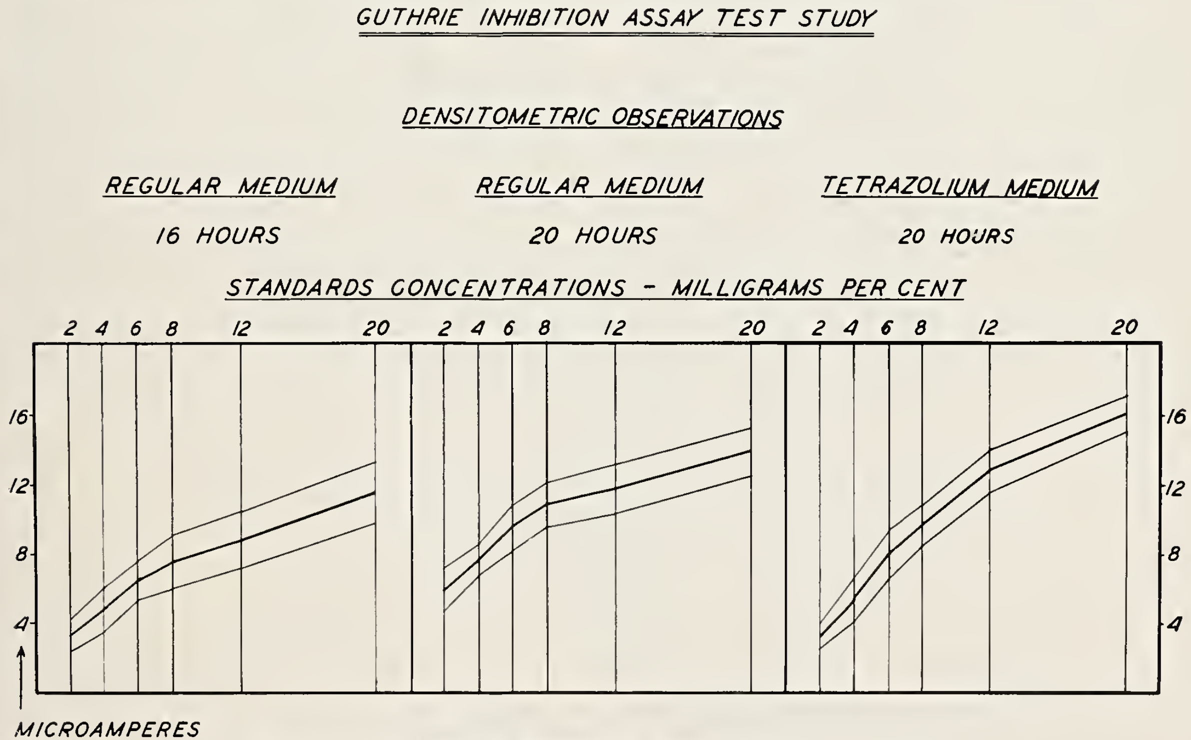


Chart 1.—Plot of Mean and Standard Deviation Values Given in Table 1.

TABLE 1.—*Densitometric Studies of Bacterial Growth Measured in Microamperes*

Standard (Per Cent)	*Values*	*Regular Medium*		*Tetrazolium Medium*
		16 Hours	*20 Hours*	*20 Hours*
	Mean	3.35	5.75	3.17
2 mg	S.D.*	0.91	1.24	0.73
	C.V.†	27.1	21.6	22.0
	Mean	4.83	7.62	5.34
4 mg	S.D.	1.31	0.96	1.31
	C.V.	27.1	12.6	24.5
	Mean	6.46	9.50	7.81
6 mg	S.D.	1.13	1.31	1.46
	C.V.	17.5	13.8	18.7
	Mean	7.53	10.78	9.60
8 mg	S.D.	1.54	1.30	1.17
	C.V.	20.1	12.1	12.2
	Mean	8.71	11.75	12.76
12 mg	S.D.	1.59	1.49	1.26
	C.V.	18.3	12.7	9.9
	Mean	11.41	13.79	16.05
20 mg	S.D.	1.73	1.39	1.06
	C.V.	15.2	10.1	6.6

*S.D.—Standard deviation.
†C.V.—Coefficient of variation.

TABLE 2.—*Standards Discrepancies*

Similar readings Standards, mg per 100 ml	*Regular Medium Read at*		*Tetrazolium Read at*
	16 Hours	*20 Hours*	*20 Hours*
2 and 4	....	....	3
4 and 6	3	1	....
6 and 8	2	3	2
6 and 12	....	1	....
6, 8, 12	2	....	....
8 and 12	7	7	....
12 and 20	2	4	....
Totals	16	16	5

Standards Discrepancies

The data obtained by densitometric observations on regular medium with 2, 4, 6, 8, 12 and 20 mg per 100 ml concentration standards, read at 16 and again at 20 hours, and on 50 tetrazolium plates with similar standards read at 20 hours, gave evidence of discrepancies in the behavior of the standards. As used here, the term *standards discrepancies* means similar densitometric readings for two (or more) standards, purportedly containing blood with different concentrations of phenylalanine. It is here emphasized that visual and densitometric observations often but not always coincide. Different "looking" standards may yield similar readings and similar "looking" standards may yield different densitometric readings, but such instances are exceptions and not the rule. We are concerned here with densitometric evaluations only. Table 2 lists standards discrepancies observed on regular and tetrazolium medium. They occurred in 16 of 50 sets of standards on regular medium and in only five of 50 sets of standards on tetrazolium medium; but the difference was due largely to discrepancies between 8 and 12 and 12 and 20 mg standards. At lower concentrations the kind of medium made no difference as to the incidence of such discrepancies.

"False Negatives" and "False Positives"

Proceeding on the assumption that MRF-AP test values are true, and taking the arbitrary stand that a GBIA test reading of 4 mg per 100 ml or more is a presumptive positive, the term "false positive" denotes a GBIA value of 4 mg or more per 100 ml with an MRF value less than 4 mg, and the term

TABLE 3.—*Comparison of Blood Phenylalanine Determinations*

Fluorometric Method*		*Guthrie† Method*		*Two Methods Agreed*	*FP*	*FN*
Mg per 100 ml	*Number*	*Mg per 100 ml*	*Number*	*(Per Cent)*	*(Per Cent)*	*(Per Cent)*
Less than 4	385	Less than 4	383	99.5	....	......
		4 or more	2	......	0.5	......
4 or more	51	Less than 4	27	......	....	53
		4 or more	24	47	....	......
4.0–4.9	14	Less than 4	14	......	....	100
		4 or more	0	......	....	......
5.0–5.9	19	Less than 4	8	......	....	42
		4 or more	11	58	....	......
6.0–6.9	10	Less than 4	5	......	....	50
		4 or more	5	50	....	......
		Less than 4	0	......	....	......
7.0 or more	8	4 or more	8	100	....	......

*Fluorometric: Manual or automated McCaman-Robins method.
†Guthrie: Guthrie bacterial inhibition assay test.
FP: False positive; FN: False negative.

false negative denotes a GBIA value of less than 4 mg per 100 ml with an MRF value of 4 mg or more. A perfect screening test should produce neither "false positive" nor "false negative" results, but of the two kinds of error it is far more important to eliminate "false negatives."

Data summarized in Table 3 were derived from studies of 236 specimens from mature infants and 200 from premature infants (prematures are a valuable source of relatively high blood phenylalanine specimens). Each of the total of 436 specimens was examined by the GBIA method and by one or more MRF methods.

There were 385 specimens with less than 4 mg of phenylalanine per 100 ml by MRF testing and 383 had GBIA values less than 4 mg per 100 ml, an agreement of 99.5 per cent. Only two had GBIA values of 4 mg per 100 ml, a 0.5 per cent incidence of "false positives."

Fifty-one specimens had MRF values of 4 mg or more per 100 ml. Twenty-four of the GBIA values were in agreement, but for 27 the values were less than 4 mg per 100 ml, a 53 per cent incidence of "false negatives." In Table 3, data for various phenylalanine levels 4 mg per 100 ml and upward by 1 mg increments are listed. For all specimens with 7 mg or more by MRF values, the GBIA values were 4 mg or more. The size of each group of samples is small and the per cent of "false negatives" might well be different with larger numbers, but there are "false negatives" with the GBIA test, especially between 4 and 7 mg per 100 ml. Therefore it becomes critically important to know how many patients with proved PKU who were studied at three days of age or less have had phenylalanine values under 7 mg per 100 ml. Using data compiled by Guthrie[6] and by Hsia and coworkers,[8] two of 24 proved PKU patients first tested at three days of age or less had less than 7 mg of phenylalanine per 100 ml. Extrapolating from our admittedly small series, there would be a 45 per cent chance of failing to detect them at this age by the GBIA method, a grave risk indeed when the harvest is one in ten thousand tests.

All data available to us indicate that persons with PKU attain blood phenylalanine levels well above 7 mg per 100 ml not long after birth—but the question is, how long? If, in using the GBIA method, 4 mg per 100 ml is employed as the level of suspicion, single tests at one week of age, or a second follow-up test within four weeks of age would probably eliminate the risk of "false negatives," based on known data.

Effects of Diet

Another possible solution involves utilization of the effects of diet. In the course of our study of premature infants, we acquired data on 44 who were given an Olac formula and 42 fed Similac. Table 4 shows that the infants who were fed Olac had a mean blood phenylalanine level of 4.53 mg per 100 ml, while for the Similac-fed infants it was 2.21 mg, the difference being highly significant. The data on the Olac-fed infants also showed that 17 were given a supplement of vitamin C, and 27 were not. The mean of blood phenylalanine levels for the 17 was 3.71 mg per 100 ml, and for the 27 it was 5.07 mg—again a significant difference. As a form of phenylalanine loading test, the first feeding of newborn infants with formula might be Olac without vitamin C for a period of 24 hours. It is recognized that feeding Olac without vitamin C supplement might lead to more "false positives," although this remains to be determined by trial on mature newborn infants.

Conclusions

Guthrie's bacterial inhibition assay test for blood phenylalanine, profoundly important to the introduction of mass screening for phenylketonuria, is a simple, cheap procedure admirably suited to private local use. Other screening methods are well suited to centralized private or public large volume studies. At the present stage of our investigations

TABLE 4.—*Effect of Diet on Blood Phenylalanine Level of Premature Infants*

Dietary Group	*Number*	*Blood Phenylalanine mean, mg per 100 ml±S.D.*	*Groups Compared*	*Diff. ± S.E. Diff.*	*S.R.*
A. Similac	42	2.21±0.41	....	....	....
B. Olac, all	44	4.53±1.79	A & B	2.32±0.28	8.4
C. Olac without vitamin C suppl.	27	5.07±1.87	A & C	2.86±0.36	7.9
D. Olac with vitamin C suppl.	17	3.71±1.11	A & D	1.50±0.75	2.0
			C & D	1.36±0.45	3.0

S.E. diff.=Standard error of the difference; S.R.=Significance ratio. It is common practice to attribute significance to differences with an S.R. of 3 or more.

they appear to be superior to the Guthrie method.

An inexpensive densitometer that was used to compare growth around standard disks on regular and tetrazolium media permits quality control. Possible slight advantages of the tetrazolium medium include smaller coefficients of variation, greater readings and fewer standards discrepancies, all at higher concentrations of phenylalanine only. Under present conditions there is a small but definite risk of "false negative" results in mass screening of infants three days of age or less by the GBIA method. Premature infants fed Olac formula without vitamin C supplement showed a considerable and significant elevation of phenylalanine as compared with those receiving the formula with vitamin C.

Pending improvement of the GBIA test, the risk of "false negative" results can be eliminated by early feeding with a high protein formula such as Olac minus vitamin C supplement, or performing a single test at an age greater than three days, or performing a second follow-up test within one month of birth.

REFERENCES

1. Conference on phenylketonuria, South Bay Pathological Society, 12 June 1965.

2. Faulkner, W. R.: Phenylalanine, in Meites. (Ed.), Standard Meth. Clin. Chem., 5:199-209, Academic Press, 1965.

3. Guthrie, R.: Blood screening for phenylketonuria, J.A.M.A., 178:863, 25 November 1961.

4. Guthrie, R., and Susi, A.: A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants, Pediatrics, 32/3:338-343, September 1963.

5. Guthrie, R., and Tieckelmann, H.: The inhibition assay: Its use in screening urinary specimens for metabolic differences associated with mental retardation, Proc. London Conf. Sc. Study Mental Def. 24 to 29 July 1960, May and Baker Ltd., Dagenham, 1962, p. 672.

6. Guthrie, R., and Whitney, S.: Phenylketonuria detection in the newborn infant as a routine hospital procedure, U. S. Dept. of Health, Welfare and Education, Children's Bureau Publication No. 419, 1964, pp. 14-16.

7. Hill, J. B., Summer, G. K., Pender, M. W., and Roszel, N. O.: An automated procedure for blood phenylalanine, Clinical Chemistry, 11/5:541-546, May 1965.

8. Hsia, D. Y., Berman, J. L., and Slatis, H. M.: Screening newborn infants for phenylketonuria, J.A.M.A., 188/3:203-206, 20 April 1964.

9. Irwin, H. R., Notrica, S., and Fleming, W.: Blood phenylalanine levels of newborn infants, Calif. Med., 101/5:331-333, November 1964.

10. McCaman, M. W., and Robins, E.: Fluorometric method for the determination of phenylalanine in serum, J. Lab. and Clin. Med., 59/5:885-890, May 1962.

11. Partington, M. W., and Sinnott, B.: Case finding in phenylketonuria: II. The Guthrie test, Canadian Med. Assoc. J., 91:105-114, 18 July 1964.

12. Scheel, C., and Berry, H. K.: Comparison of serum phenylalanine levels with growth in Guthrie's inhibition assay in newborn infants, J. Pediatrics, 61/4:610-616, October 1962.

Pulmonary Artery Stenosis

A Frequent Part of the Congenital Rubella Syndrome

JOSEPH G. ELLIS, M.D., AND WILLIAM J. KUZMAN, M.D., *San Diego*

■ *The case records, cardiac catheterization and angiographic findings in 32 patients were reviewed to illustrate the high incidence of pulmonary artery stenosis in congenital rubella syndrome. These interesting lesions often are of equivocal or unknown clinical significance compared with the other malformations that beset these patients, but to know of them explains certain physical findings and to study their incidence is an unusual opportunity to pinpoint a definite cause for a congenital cardiac lesion.*

CAMPBELL[2] HAS SAID that patent ductus arteriosus is the most common cardiac malformation met in congenital rubella syndrome. Recently Rowe[8] and Emmanouilides[5] have reported an equally frequent finding, stenosis of the main pulmonary artery branches. Either one or both pulmonary arteries may be discretely narrowed, usually at their origin from the main trunk, and the lesions may occur by themselves or accompanying other cardiac defects. These are uncommon lesions within the population of patients with congenital heart disease,[4,7] but within the population of patients with congenital heart disease due to maternal rubella infection, pulmonary artery stenosis seems to be common. This report describes this coincidence from the experience of the cardiac catheterization laboratory of a general hospital gained through studies on such patients with congenital rubella and pulmonary artery branch stenosis.

Materials and Methods

During the eight-year period 1958-1966, 821 infants, children, or young adults were referred to this center because of a suspicion of congenital heart disease. Twenty of them were regarded as having congenital rubella syndrome because there was a history of maternal rubella infection during pregnancy or there were grounds for suspecting such infection may have occurred and the patient had other congenital anomalies such as cataracts, deafness, mental retardation, microcephaly or microphthalmia.

Also 22 of the 821 patients had pulmonary artery stenosis either as an isolated lesion or combined with other cardiac defects. The diagnosis of pulmonary artery stenosis was based on hearing a systolic murmur originating in the pulmonic area and radiating to the axillae and both sides of the back, recording a sharply localized pressure gradient on pull-through tracings from within the main pulmonary artery branches, and seeing a narrowing on the pulmonary angiogram. In most instances all these conditions were met, but in some cases where cardiac catheterization seemed unnecessary or inadvisable, the diagnosis was based

---

From the San Diego County Heart Center, Donald N. Sharp Memorial Community Hospital, San Diego, and the Scripps Clinic and Research Foundation, La Jolla.

This study was supported in part by NIH Graduate Training Grant No. 5513-03.

Submitted 6 June 1966.

Reprint requests to: Scripps Clinic and Research Foundation, La Jolla, California 92038 (Dr. Ellis).

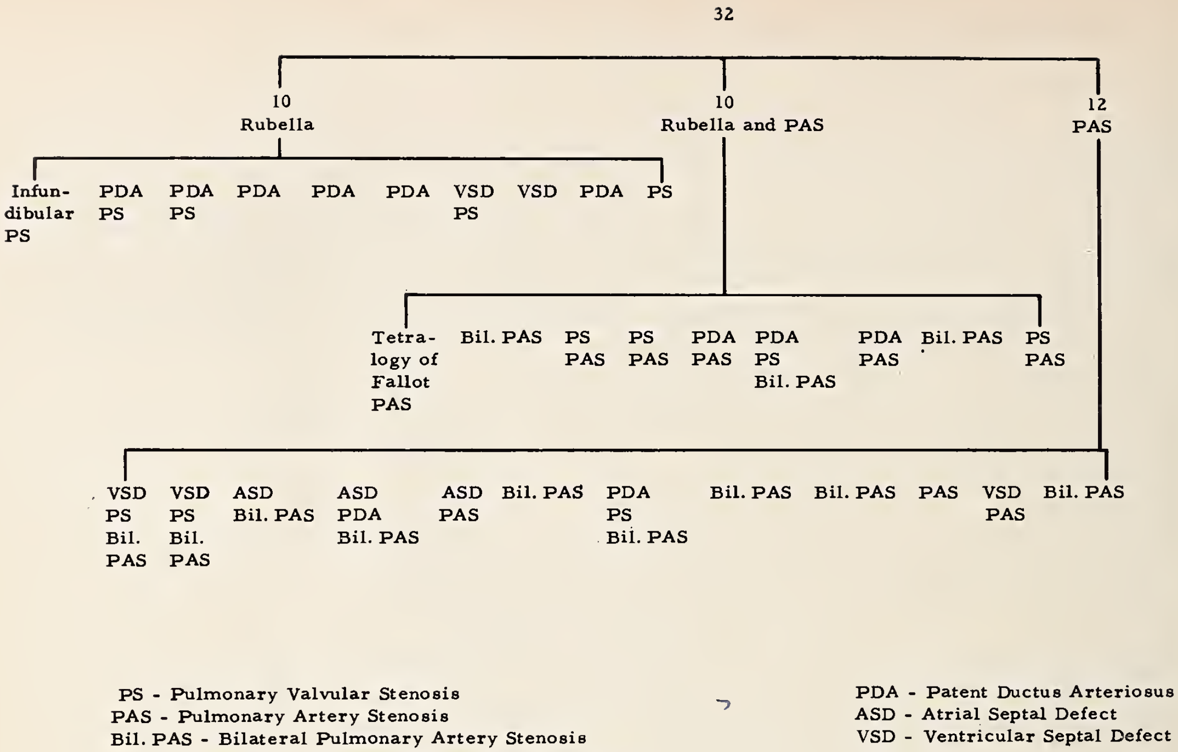


Chart 1.—Cardiovascular lesions in 32 patients with congenital heart disease.

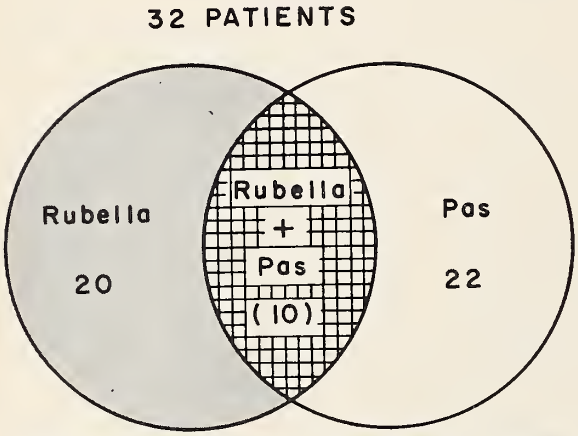


Chart 2.—Overlap between patients having congenital rubella syndrome and pulmonary artery stenosis.

solely on physical findings. Ten of these 22 patients were also in the group having congenital rubella syndrome (Charts 1 and 2).

Results

Twenty patients had congenital rubella syndrome (Tables 1 and 2). Ten of these had stenosis at one or more sites in the main pulmonary artery branches. There were 12 other patients with pulmonary artery stenosis who had no history or evidence of congenital rubella (Table 3). Accompanying cardiac lesions in the patients with rubella syndrome included patent ductus arteriosus (nine cases), pulmonary valvular stenosis (two cases), pulmonary infundibular stenosis (two cases), ventricular septal defect (two cases), and tetralogy of Fallot (one case). Accompanying cardiac lesions in the patients without rubella syndrome included atrial septal defect in three, patent ductus arteriosus in two, pulmonary valvular stenosis in two, ventricular septal defect in one, and acyanotic tetralogy of Fallot in two.

Seven of the patients with bilateral pulmonary artery stenosis showed a characteristic pulmonary trunk pressure curve described by Agustsson and coworkers[1,3] (Figure 1).

In general the stenotic lesions of the pulmonary arteries presented no urgent clinical problems. Surgical repair was attempted in two cases, successfully in a four-year-old girl (Case 13) who benefited from patch grafting of the right pulmonary artery and pulmonary valvotomy, and unsuccessfully in a two-year-old boy (Case 30) with hypoplastic pulmonary arteries and a pressure gradient of 85 mm of mercury between the branches and the main pulmonary artery trunk.

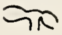
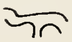
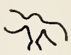
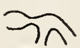
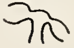
On physical examination the usual finding was a grade II to IV ejection systolic murmur in the second to third intercostal space to the left of the sternum with wide radiation to both axillae and over the posterior chest to both the right and left sides. In patients with isolated stenotic lesions the second sound in the pulmonic area was either normal or moderately split—0.04 to 0.06 seconds—and varied with respiration (Figure 2). The electrocardiograms were consistent with incomplete and complete right bundle branch block and right ventricular hypertrophy. Often an associated le-

TABLE 1.—*Congenital Rubella Syndrome without Pulmonary Artery Stenosis*

Case No.	*Age at First Visit*	*Sex*	*Cardiac Defects*	*Other Defects*	*Remarks*
1	13 years	F	Infundibular Pulmonary stenosis	Deafness Mental Retardation	....
2	3 years	F	PDA PS	Bilateral Cataracts	PDA ligated at age 4
3	3 years	M	PDA PS	Bilateral nerve deafness	PDA ligated at age 2 months
4	1 year	M	PDA	Bilateral cataracts & deafness	PDA ligated at age 1 year
5	10 days	M	PDA	Convulsive disorder	PDA ligated at age 10 days
6	4 months	F	PDA	Convulsive disorder, bilateral cataracts, microcephaly	....
7	2 months	M	VSD PS	Cataract O.D.	....
8	3 years	F	VSD	Micropthalmia O.S.	VSD repaired at age 3 years
9	10 months	M	PDA	Mental retardation	....
10	5 months	F	Probable infundibular Pulmonary stenosis	....	....

PAS=Pulmonary artery stenosis.
PS=Pulmonary valvular stenosis.
PDA=Patent ductus arteriosus.
ASD=Atrial septal defect.
VSD=Ventricular septal defect.

TABLE 2.—*Congenital Rubella Syndrome with Pulmonary Artery Stenosis*

Case No.	*Age at First Visit*	*Sex*	*Cardiac Defects*	*Other Defects*	*Pressures mm Hg*			*Angio-gram*
					MPA	*RPA*	*LPA*	
11	6 years	F	Bilateral PAS	Deafness	43/7	16/8	15/7	
12	2 years	F	PS PAS	Deafness Clubbed feet	......	......	......	......
13	4 years	F	PS PAS	Bilateral nerve deafness	70/14	27/14	......	
14	2 months	F	PDA PS	Cataract O.S.	......	......	......	......
15	3 years	F F	PDA PAS Aberrant right subclavian	....	33/10	15/10	......	......
16	2 years	F	PDA PS Bilateral PAS	Cataracts & deafness	37/9	19/13	18/11	
17	9 days	F	....	....	......	......	......	
18	11 years	F	Bilateral PAS	....	53/6	20/9	20/10	
19	3 months	F	PAS	....	......	......	......	......
20	10 years	M	Tetralogy of Fallot PAS	Deafness	......	......	......	......

REMARKS—TABLE 2

12. Physical findings characteristic with Gr. II ejection systolic murmur radiating to both axillae and right back.
13. Repair coarctation right pulmonary artery and pulmonary valvotomy at age 4.
14. PDA ligated at age 3 months, systolic murmur radiating over the back persisted.
15. PDA and aberrant right subclavian artery ligation.
17. Ligation PDA at 2 weeks of age.
19. Physical findings characteristic with Gr. II ejection systolic murmur radiating to both axillae and back.
20. Open repair of tetralogy of Fallot at age 4. Persisting systolic murmur radiating to both axillae and back.

sion produced the pattern of biventricular enlargement. X-ray films of the chest were also nonspecific, showing either cardiac enlargement or cardiac enlargement with prominence of the main pulmonary artery.

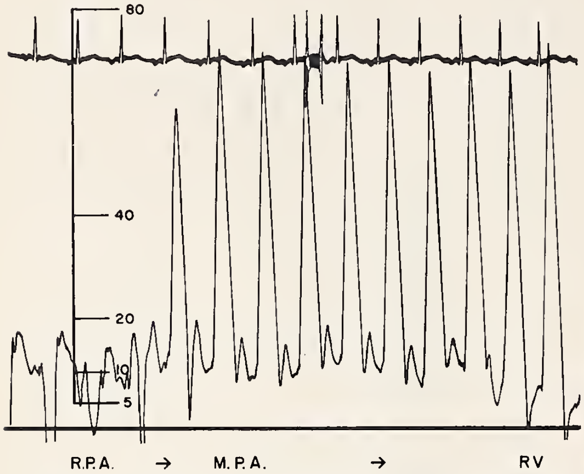


Figure 1.—(Case 18 in Table 2). Pressure curves recorded as the catheter traversed the left pulmonary artery and main pulmonary trunk to the right ventricle. The patient was an 11-year-old girl with bilateral pulmonary artery stenosis.

Discussion

After reviewing his own experience and that of others, Campbell[2] decided that between 1 and 2 per cent of congenital heart disease was caused by congenital rubella syndrome. The incidence in the present series (20 of 821 patients) was 2.4 per cent, which is in fairly close accord. D'Cruz and coworkers[3] reported 84 of 2,000 patients (4.2 per cent) were found to have stenosis of one or several areas in the main pulmonary artery or its

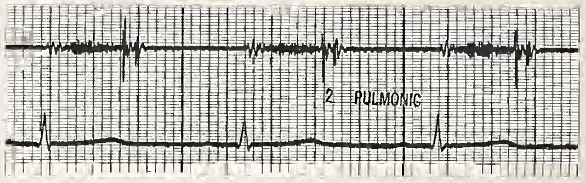
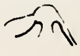
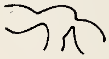
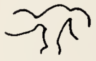
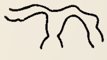
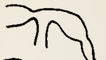
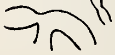
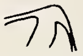
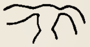
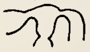


Figure 2.—Phonocardiogram recorded from the pulmonic area in patient with bilateral pulmonary artery stenosis (Case 18, Table 2). There is a systolic ejection murmur and the second sound is split 0.06 second.

TABLE 3.—*Pulmonary Artery Stenosis without Congenital Rubella Syndrome*

Case No.	*Age at First Visit*	*Sex*	*Cardiac Defects*	*Pressures mm Hg*			*Angiogram*	*Remarks*
				MPA	*RPA*	*LPA*		
21	7 years	M	ASD, partial anomalous pulmonary venous drainage to innominate vein, bilateral PAS	43/9	27/10	......		ASD repaired at age 8
22	7 years	F	ASD, PDA, bilateral PAS	45/17	28/11	......		PDA ligated at age 2
23	11 years	F	ASD	32/10	18/10	......	....	ASD repaired at age 11
24	4 years	F	Bilateral PAS	30/13	17/12	16/12	....	....
25	5 years	F	PDA, PS, bilateral	80/15	22/14	......		Ligation PDA, pulmonary valvotomy at age 5
26	11 years	F	anomalous subclavian artery, hypoplastic descending aorta. PS, bilateral PAS (hypoplastic & tortuous pulmonary arteries)	30/9	17/9	......		....
27	22 years	M	Bilateral PAS	70/18	43/20	30/15		....
28	7 years	M	PAS	32/6	21/6	......		....
29	3 years	M	VSD, PAS	80/32	58/25	......	....	VSD repaired at age 3
30	2 years	M	Bilateral PAS (Hypoplastic)	100/13	15/8	15/5		Died at operation at age 2
31	1 year	F	VSD, PS, bilateral PAS	30/18	23/15	20/13		....
32	11 years	F	VSD, PS, bilateral PAS	30/12	18/11	22/10		....

branches. The incidence of this condition in the present series was 2.7 per cent (22 to 821 patients). The remarkable observation in this series is the overlap between these groups, making it possible to say that 50 per cent of the patients with congenital rubella syndrome were found to have pulmonary artery stenosis as some part of their cardiac malformation and that among patients found to have pulmonary artery stenosis almost half had congenital rubella syndrome.

Rowe's[6] remarks on this association sprang from an experience with a rubella epidemic in New Zealand. In his report published in 1963[8] he discussed 35 patients with congenital rubella syndrome, 11 of whom had pulmonary artery stenosis. As the obverse, he also mentioned 18 patients with pulmonary artery stenosis, in 11 of whom the lesion was associated with congenital rubella. Since specific questioning about maternal rubella infection was part of history taking in the San Diego County Heart Center during the eight-year period reviewed, the fact that the majority of the patients in the series are young is due to a similar epidemic of rubella that occurred in many parts of this country in recent years.

Why rubella virus has such a predilection for the structure of the embryologic sixth dorsal arch is not known, but it is certainly true that patent ductus arteriosus and pulmonary artery stenosis far exceed valvular and septal defects in this infection.

REFERENCES

1. Agustsson, M. H., Arcilla, R. A., Gasul, B. M., Bicoff, J. P., Nassif, S. I., and Lendrum, B. L.: The diagnosis of bilateral stenosis of the primary pulmonary artery branches based on characteristic pulmonary trunk pressure curves, Circulation, 26:421, 1962.

2. Campbell, Maurice: Causes of malformations of the heart, Brit. Med. J., 2:895, 1965.

3. D'Cruz, I. A., Agustsson, M. H., Bicoff, J. P., Weinberg, M., Jr., and Arcilla, R. A.: Stenotic lesions of the pulmonary arteries, Am. J. Cardiol., 13:441, 1964.

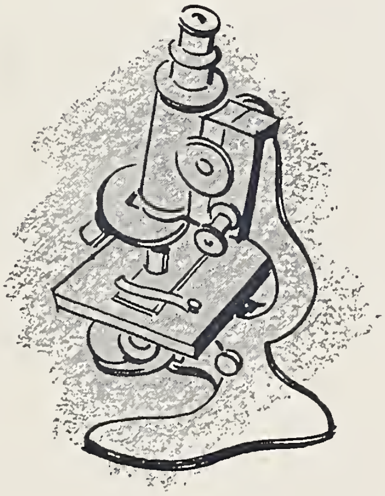
4. Delaney, T. B., and Nadas, A. S.: Peripheral pulmonic stenosis, Am. J. Cardiol., 13:451, 1964.

5. Emmanouilides, G. C., Linde, L. M., and Crittenden, I. H.: Pulmonary artery stenosis associated with ductus arteriosus following maternal rubella, Circulation, 29:514, 1964.

6. Liggins, G. C., and Phillips, L. I.: Rubella embryopathy, Brit. Med. J., 1:711, 1963.

7. McCue, C. M., Robertson, L. W., Lester, R. G., and Mauck, H. P., Jr.: Pulmonary artery coarctations, J. Pediat., 67:222, 1965.

8. Rowe, R. D.: Maternal rubella and pulmonary artery stenoses, Pediatrics, 32:180, 1963.



Bovine Bile Derivative Treatment For Cancer

A Critical Evaluation

HAROLD MASTERS, M.D., *Beverly Hills*, JOEL SOLOMON, M.D., *Duarte*, JOSEPH R. BATEMAN, M.D., *Los Angeles*, HAROLD BERNSTEIN, M.D., *Beverly Hills*, AND ERNEST BEUTLER, M.D., *Duarte*

■ *Bovine bile derivative, a material reported to be effective in cancer chemotherapy, was administered to 31 patients with malignant disease. In 22 cases the results were considered evaluable. In one of the 22 there was a suggestion of antitumor response. In almost all patients diarrhea and phlebitis developed and in 11 these complications necessitated cessation of therapy.*

IN 1963, Penn[1] published a method of preparing a bovine bile derivative (BBD) and reported that 18 of 26 patients with various types of inoperable malignant neoplasm who were treated with it were improved. Consequently there has been considerable interest in BBD in both professional and lay circles. To determine whether this agent has a place in cancer chemotherapy, an inter-institutional cooperative study was devised for the critical evaluation of the clinical effects of this preparation.

Methods

The BBD used in this program was prepared according to the specifications of Penn by Calbiochem, Los Angeles, California. Patients with incurable cancer whose lesions were objectively measurable and who had received no recent antitumor therapy were selected. The protocol, which was prepared in consultation with Penn, stipulated that each patient should receive 100 mg of BBD per kg of body weight by intravenous infusion daily for the first seven days, and then three times weekly during the second through seventh weeks. After the completion of the seventh week, each patient was to receive 1 gm by mouth daily. During the course of the study, leukocyte count, hematocrit, platelet count, urinalysis, blood urea nitrogen, serum bilirubin, serum transaminases, and serum alkaline phosphatase determinations, appropriate x-rays, measurements of tumor size and the patient's clinical status were evaluated at specified intervals.

Results

Thirty-one patients began treatment under this protocol. Of these, only 17 received more than 2,000 mg of BBD per kg total dose and are considered to have completed the course of therapy. Of the 14 patients who did not complete therapy, three died from their tumors, and therapy had to be

---

From the City of Hope Medical Center, Duarte, the John Wesley County Hospital and the University of Southern California School of Medicine, Los Angeles.

This study was supported by the Trattner Research Foundation and by U.S. Public Health Service Grants CA 07585 and CA 05186 from the National Cancer Institute. It was planned by the Scientific Advisory Board of the Trattner Research Foundation: Drs. J. R. Bateman, H. Bernstein, E. Beutler, N. B. Kurnick, H. Masters, and M. A. Rawitch.

Submitted 20 April 1966.

Reprint requests to: City of Hope Medical Center, 1500 East Duarte Road, Duarte 91010 (Dr. Solomon).

discontinued in six instances because of severe diarrhea and in five because of phlebothrombotic complications. Five of these patients received between 1,000 and 2,000 mg of BBD per kg and are also assumed to be evaluable. The nine patients who received less than 1 gm per kg are classified as unevaluable. In addition to the intravenous therapy, 13 patients received 40 to 2,030 mg of BBD per kg by mouth over periods ranging from 4 to 122 days.

Of the patients who received more than 2,000 mg per kg, two had adenocarcinoma of the uterus, two carcinoma of the stomach, one mixed carcinoma of the lung, one anaplastic carcinoma of the lung, two adenocarcinoma from unknown primary sites, one solitary myeloma, four carcinoma of the breast, one carcinoma of the maxillary sinus, one neurofibrosarcoma, one carcinoma of the rectum, and one carcinoma of the prostate gland. One patient with adenocarcinoma of the uterus, one with squamous cell carcinoma of the lung, two with carcinoma of the breast, and one with carcinoma of the colon received between 1,000 and 2,000 mg per kg.

In only one person in the entire group of 31 studied was there any suggestion of antitumor effect:

The patient was a 73-year-old white woman who had had total hysterectomy on 7 November 1963 for adenocarcinoma of the uterus. On 6 July 1965, vaginal examination revealed a 2 cm ulcerated lesion in the left upper vaginal vault. A surgical biopsy specimen on that date contained adenocarcinoma. On 7 July, BBD therapy was initiated according to the protocol. During intravenous therapy the patient had recurrent peripheral phlebitis and diarrhea, which were controlled by symptomatic measures. After one month of intravenous therapy, a reexamination of the vaginal vault revealed that the lesion had decreased to about one-third its original size. Biopsy on 26 August showed no evidence of tumor, and repeated vaginal examinations from 29 September to the present* have failed to demonstrate any lesion. No significant change in the clinical status of the patient has been noted.

The most frequent toxic effects noted were diarrhea and phlebitis of the veins in which the infusions were given. Diarrhea occurred in 28 of the 31 patients and phlebitis in 30. In one patient a superior caval syndrome developed, with evidence on venogram of obstruction of the superior vena cava, after he had received 600 mg per kg in six days through an indwelling catheter extending into the left subclavian vein plus 100 mg per kg in one day through a catheter in the right subclavian system. Another patient who received 270 mg per kg in three days through a left femoral vein catheter was demonstrated on venogram to have obstruction of that vein and possibly of the inferior vena cava. Other side effects that were noted from intravenous BBD therapy were nausea in four subjects, vomiting in one, abdominal pain in one and dysphagia in two. Two patients had local reactions, with pain at the site of injection in one and ulcerations in an area of extravasation in the other. Anuria in one subject and transient leukopenia in another were probably not related to the drug. The only side effect noted from the oral preparation of BBD was epigastric pain in one patient with gastric carcinoma.

Discussion

Of the 26 patients with assorted malignancies who were reported upon by Penn in 1963, 21 were treated in India under the auspices of Dr. R. Viswanathan, and five in private practice in this country. Eighteen of these 26 persons were said to be improved by therapy. The preparation was found to be non-toxic with only two side effects encountered: Transitory diarrhea and sclerosis of the veins at the site of repeated injection.

Using the dose schedules recommended by Penn, we have been unable to reproduce these results. Of the 22 patients that we believe to be evaluable, only one had a response that could in any way be considered to be an antitumor effect. This patient had only a very small solitary ulcerated lesion from which a biopsy specimen had been taken the day before the start of BBD therapy. Although, as Penn indicated, the principal side effects were diarrhea and phlebitis, these disorders were sufficiently severe in 11 cases in the present study to necessitate discontinuing the agent, and in two instances the phlebitis resulted in obstruction of major vessels.

We have concluded, therefore, that BBD has no demonstrable merit in the treatment of malignant disease, that it is difficult to administer, and that it has significant toxicity.

REFERENCE

1. Penn, H. S.: Management of the patient with inoperable carcinoma, J. Int. Coll. Surg., 39:335-340, April 1963.

---

*1 November 1966.

REVIEW ARTICLE

Advances in the Theory and Practice of Exchange Transfusions

RODERIC H. PHIBBS, M.D., *San Francisco*

■ *In the management and prevention of hemolytic disease of the newborn, exchange transfusions seem destined to remain the mainstay of therapy for some time to come.*

Our current knowledge of bilirubin metabolism has altered the indications for the procedure and introduced such useful new adjuncts to therapy as albumin infusions. The decision to do an exchange transfusion cannot be made by any one rule, but must be individualized for each patient and take into account all the factors known to influence the risks of bilirubin toxicity and the exchange procedure. A thorough evaluation of the infant's condition, particularly his cardiorespiratory and metabolic status (including blood pH, gas and albumin determinations), will provide valuable information as a guide to therapy. The limited capacity of some newborn infants to make adequate physiological adaptations to a variety of stresses imposed by the procedure influences the preparation of donor blood, the rate and volume of exchange and the time at which it should be done.

A clear understanding of the mechanics of the exchange and the distribution of indirect bilirubin within the body will permit more accurate prediction of what can be accomplished in bilirubin removal and correction of hematocrit with exchanges of different volumes. When weighing the risk of kernicterus against that of exchange transfusion, the experience of the operator and the availability of suitable facilities cannot be ignored.

EXCHANGE TRANSFUSION, the mainstay for the treatment of hemolytic disease of the newborn (HDN) for the past two decades, can achieve three things: (1) With sedimented red cells, it can raise the hematocrit without increasing the blood volume of a severely affected erythroblastotic newborn infant in the first minutes of life; (2) It can remove antibody-coated cells from the involved newborn infant's circulation before they hemolyze and produce bilirubin; and (3) It can remove bilirubin in the circulating plasma and some from extravascular areas, so that its concentration can be kept below levels which are generally considered to be toxic to tissues—particularly central nervous system tissues.* New diagnostic and therapeutic

---

From the Department of Pediatrics, University of California San Francisco Medical Center.

Reprint requests to: Department of Pediatrics, University of California San Francisco Medical Center, 94122.

*Direct van den Bergh reacting bilirubin or glucuronide conjugated bilirubin is considered to be non-toxic. Indirect reacting or unconjugated bilirubin is the dangerous fraction, and throughout this paper *bilirubin* refers only to this fraction. The importance of a uniform laboratory standard for indirect bilirubin has been emphasized recently.[2]

developments include amniocentesis, intraperitoneal transfusion and prevention of maternal sensitization.

Amniocentesis. Spectrophotometric analysis of amniotic fluid obtained by amniocentesis permits accurate prediction of the presence of isoimmune hemolytic disease in the fetus, assessment of severity of disease, and prediction as to which infants should be delivered before 40 weeks of gestation to prevent intrauterine death.[9]

Intrauterine intraperitoneal transfusions are used for severely affected fetuses to keep them alive and healthy long enough so that the pregnancy may be carried to a point where the newborn infant will not be too small or anemic and hydropic to be saved.[10,11] A few fetuses that receive intrauterine transfusions absorb so much of the donor blood into the circulation that erythropoiesis is suppressed; there are no Rh-positive cells in their circulation to be hemolyzed to produce bilirubin, so that they do not need exchange transfusions. Most of these infants, however, need multiple exchange transfusions after birth.

Intrauterine transfusions of moderately affected fetuses might eliminate the need for many exchange transfusions after birth; however, this would replace a relatively safe and highly effective form of therapy with one which still carries a high fetal mortality and is rightly reserved for only the desperately ill fetus.

Maternal sensitization. Injection of anti-Rh antibodies into Rh-negative mothers with Rh-positive husbands is being studied as a means of preventing maternal sensitization and production of massive amounts of antibodies.[6] This offers hope for preventing HDN and eliminating the need for most exchange transfusions. But, even if effective, a massive program would have to be carried out before there was a population free of sensitized Rh-negative mothers, and it would not eliminate isoimmunization due to other blood groups.

Indications for Exchange Transfusion

The first consideration in exchange transfusion is the indication for the procedure itself. If an affected baby at birth is significantly anemic, is hyperbilirubinemic and has increased concentrations of reticulocytes and nucleated red cells in the peripheral blood, kernicterus is likely to develop unless an exchange transfusion is performed. These infants must have an exchange transfusion in the first two to 24 hours of life, and may require a *small* exchange with sedimented erythrocytes in the first few hours of life if the anemia is severe enough to produce signs and symptoms of cardiorespiratory embarrassment.

Most infants, however, are not so severely affected. The objective is to keep the concentration of bilirubin at so low a level that the chance for kernicterus to develop is no greater than the risk of the exchange procedure itself. The higher the peak level of bilirubin, the greater the chances for kernicterus.[1] The key question, then, is: What is the level of bilirubin at which the chances that kernicterus will develop, equal or surpass the possibility of death due to the procedure itself (which should be about 1 per cent or less in term infants without hydrops or respiratory distress)? This is still a controversial question. The toxic effects of indirect bilirubin upon the central nervous system are a function of a variety of physiological variables in addition to the plasma concentration of bilirubin.

There is as yet insufficient clinical data to evaluate the relative importance of each variable. McKay[12] has summarized the problem as follows:

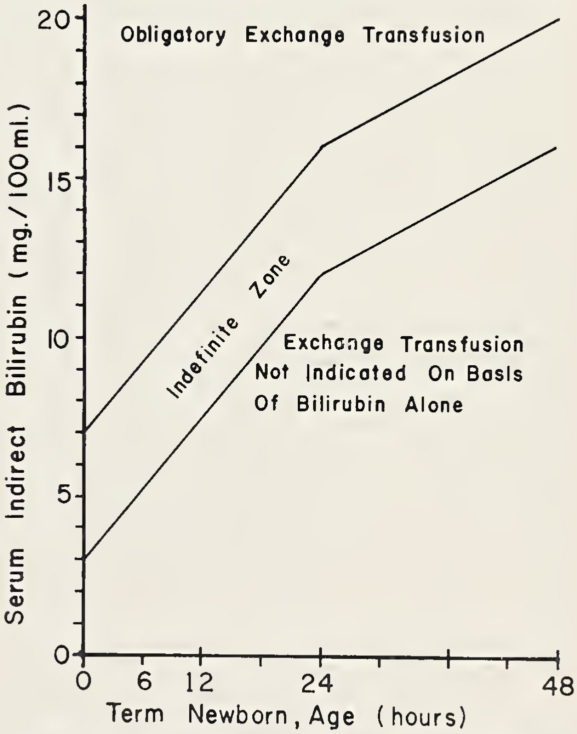


Chart 1A.—Chart for using serum indirect bilirubin concentrations as the sole indication for exchange transfusion in mature infants. An infant with hemolytic disease of the newborn and indirect bilirubin measurements above the upper line is a candidate for exchange transfusion on the basis of the bilirubin alone.

"The only absolute indication for exchange transfusion is the appearance of clinical signs of *early* kernicterus, whatever the level of serum bilirubin." He is quick, however, to point out that clinicians must use the available but incomplete data to evaluate the risk of kernicterus in each individual patient in terms of all the variables.

Bilirubin. The critical concentration of bilirubin is not in the plasma but within the cell, where its toxic properties interfere with oxidative metabolism—probably by a toxic effect upon the mitochondria.[13] Though plasma and intracellular concentrations of bilirubin are related, one is not a direct measurement of the other. Much of the extracellular bilirubin is bound to albumin and does not enter a cell easily. By raising the concentration of albumin to a level at which its bilirubin-binding capacity exceeds the amount of bilirubin present, bilirubin will be prevented from going into cells and its toxic effect will be blocked. At such concentrations of albumin, intracellular bilirubin is drawn out slowly into the extracellular fluid.[5,20] Even the intracellular concentration may have a variable toxicity, depending upon the condition in the individual cell—a hypoxic or acidotic cell may be more sensitive.

Originally, clinical evaluation in hemolytic disease due to Rh or ABO incompatibility correlated the peak level of serum bilirubin, the severity of hemolysis and maturity with the chances for kernicterus.[1] The critical level of bilirubin concentration was considered to be 20 mg per 100 ml in full-term newborns and 18 mg per 100 ml in prematures; below these levels, the chances for kernicterus to develop were less than 5 per cent, perhaps as low as 2 to 3 per cent. Allen and Diamond[1] developed a useful chart for plotting serial determinations of bilirubin within the first 12 or 24 hours of life which indicated whether a baby would ultimately reach a concentration over 20 mg per 100 ml and require an exchange transfusion (Charts 1A and 1B).

Normal adult plasma has enough albumin to bind approximately 80 mg of bilirubin per 100 ml,[14] but the binding of bilirubin by albumin varies directly with pH and is diminished by other com-

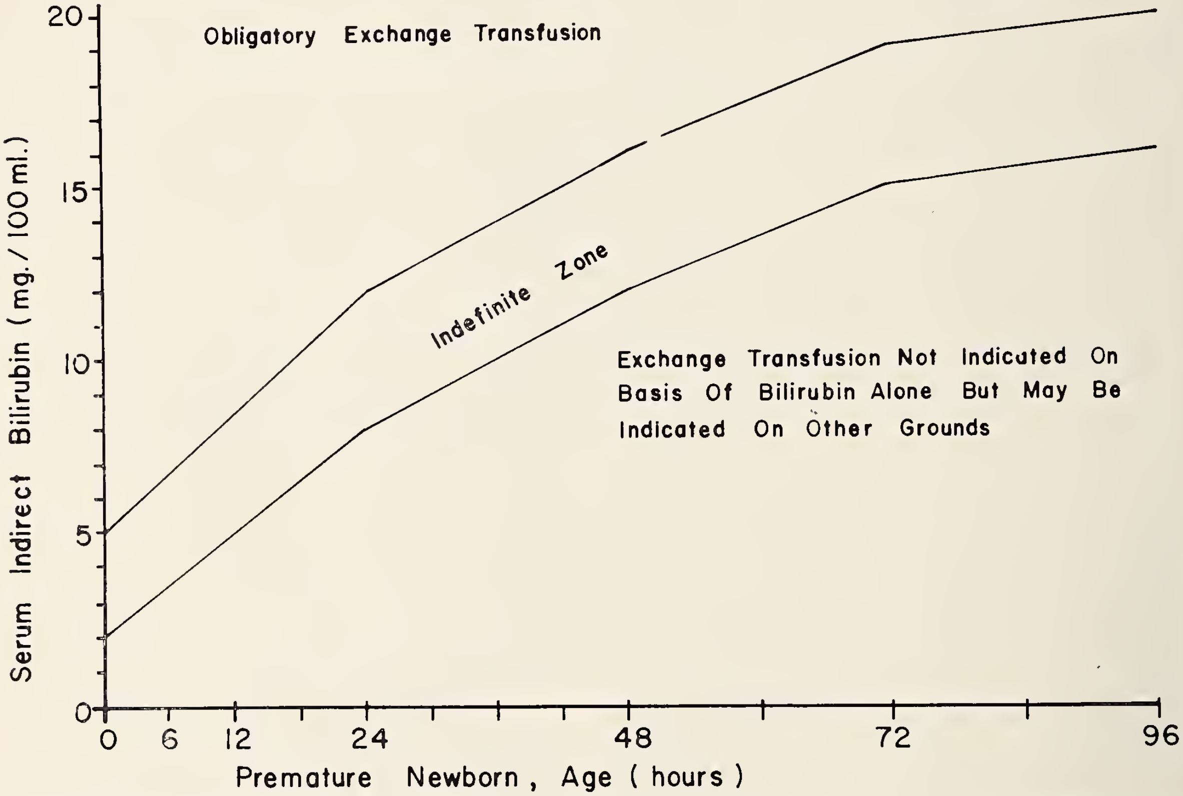


Chart 1B.—Chart for premature infants with hemolytic disease of the newborn. This chart and Chart 1A are meant to be tentative guides only. The indications for exchange transfusion which they define should be modified by the clinical findings and other laboratory studies on the individual patient. (Charts after Allen and Diamond, with the kind permission of Dr. F. H. Allen.)

pounds which bind competitively with albumin (sulfonamides, free fatty acids,* salicylates and certain other antimicrobial agents). Newborn infants have a low concentration of albumin. They are often acidotic and the pH of the extracellular fluid adjacent to a cell may be considerably less than in arterial blood, particularly in those cells at a distance from the nearest capillary. If peripheral circulation is poor, local metabolic acidosis will further lower the bilirubin-binding capacity of the albumin. Thus, acid base balance, regional microcirculation, presence of competitive binding substances and lower levels of albumin may make a given concentration of bilirubin much more toxic in one infant than in another.

Porter and Waters, attempting to improve criteria for doing exchange transfusions, measured the capacity of a given specimen of serum to bind more bilirubin.[17,21] So long as there is some residual binding capacity, the infant is presumed to be protected from the toxic effects of bilirubin. This measurement is more nearly definitive than that of serum bilirubin and albumin, but it has a serious drawback. What is actually measured is the capacity of plasma to bind a dye, not more bilirubin. The test is done at a pH of 7.4 and the binding of the dye is uninfluenced by changes in pH. This test might indicate a given bilirubin level was safe because at pH 7.4 an infant's plasma had the capacity to bind more bilirubin than was present. However, at the pH of the infant's blood, the binding capacity may have been exceeded and the bilirubin actually at a dangerous level. The laboratory value alone, therefore, cannot be taken as an indication for exchange transfusion, and the general condition of the infant must still be taken into account.

Cause of hyperbilirubinemia. The original data on the risk of kernicterus are for hyperbilirubinemia due to Rh and ABO-isoimmune hemolytic disease. At a given level of severity, disease due to ABO incompatibility is probably just as dangerous as Rh hemolytic disease.[1] Higher levels of bilirubin may be safe in ABO disease, but data are too scant to accept this dangerous assumption as an operating principle. Hemolytic diseases due to less common fetal-maternal incompatibilities, such as maternal anti-Kell, are not common enough to be evaluated separately at this time and should be considered as dangerous as Rh or ABO hemolytic disease.

Kernicterus due to non-hemolytic hyperbilirubinemia is well documented and can occur in prematures at low concentrations of bilirubin.[3,12] However, under equivalent conditions, a given concentration of bilirubin as the result of hemolytic disease seems to be more toxic than the same concentration due to other causes.[22] There are a number of possible explanations for this.

In isoimmune hemolytic disease of the newborn (HDN) the infant's erythrocytes are coated with maternal globulin which interferes with oxygen transport across the cell membrane. Furthermore, the breakdown products of hemoglobin released by hemolysis are present in higher concentrations. Carboxyhemoglobin may have a toxic effect upon the brain tissue, and heme products that are bound to albumin as methemalbumin may interfere with bilirubin binding.

Age. It has been suggested that with age the newborn's blood brain barrier may change so that bilirubin is no longer toxic and that, therefore, exchange transfusions are not needed after about five days of age. On the other hand, there is some evidence from animal experimentation that, under equivalent conditions, bilirubin enters brain tissue just as easily in adults as in newborns.[5] Clinically, kernicterus has been observed to develop after the first one or two weeks of life. The rarity of such cases is explained by the facts that (1) Such high levels of indirect bilirubin are seldom seen after the first week of life, and (2) By this age, those factors which enhance bilirubin toxicity are much less common. For the time being, one cannot consider bilirubin to be non-toxic at any level after the first week of life.

If all the critical factors and the relative importance of each variable were known, one could predict which 5 per cent of all full-term infants would develop kernicterus when the serum bilirubin exceeded 20 mg per 100 ml, which infants would be safe at a much higher level, and which were in danger at levels below it. Only some of these factors are known at present, but they are being used to alter the criteria for exchange transfusion.

Present criteria vary considerably from one medical center to another. The following is an attempt to summarize them.

In HDN due to Rh, ABO or any other incompatibility, the old standards (with modifications) still apply: In infants under two days of age, bilirubin levels are kept below 20 mg per 100 ml in full-term newborns and 18 mg per 100 ml in prematures; from two to five days of age (10 days for small prematures) the same standards apply, except that the critical level of bilirubin should be found on two successive determinations four hours apart. (Other observers use 22 mg per 100 ml as the critical level in healthy full-term newborn infants.) The concentration at birth and the early rise of bilirubin (Charts 1A and 1B), the presence of such other findings as anemia (hemoglobin less than 11 gm per 100 ml) or hydrops, and previous maternal history* are guides for early exchange transfusion. The critical concentration for exchange transfusion is lowered by at least 2 to 4 mg per 100 ml in the presence of any of the factors known to increase the chance of bilirubin toxicity. However, the most common aggravating factors (the respiratory distress syndrome with its consequent hypoxia, acidosis and poor peripheral circulation) also make transfusion a more hazardous procedure.

---

*These are elevated when an infant has no source of carbohydrate.

In non-hemolytic jaundice, the critical level is about 5 mg per 100 ml higher than in similar infants with HDN—that is, 20 or 23 mg per 100 ml in healthy prematures and up to 25 mg per 100 ml in healthy full-term babies. Again the critical level is lowered by the presence of acidosis. Early signs of kernicterus are an indication for exchange transfusion regardless of the concentration and cause hyperbilirubinemia. (Lethargy, poor sucking, hypotonia and a poor Moro response generally precede the more classic and specific signs of fever, opisthotonos, high-pitched cry and a "sunset" appearance of the eyes.)

Donor Blood

Once exchange transfusion is decided upon, the appropriate donor blood should be available immediately so that the exchange can be done and, if necessary, repeated at the optimum time. The physician should not, at that late date, begin to arrange for an appropriate unit or units of donor blood. Bilirubin levels can rise to dangerous levels during a belated search for appropriate donor blood. If a woman has a history of babies affected with Rh hemolytic disease, or if evaluation of the amniotic fluid suggests moderate or severe hemolysis, packed or sedimented red cells and whole blood should be ready at the time of her infant's birth.

Compatibility. The first consideration in the selection of donor blood is immunocompatibility to insure that the red cells in the donor blood are compatible with all the maternal antibodies which may have crossed the placenta into the fetus.[1] The cross-match must always be done against maternal serum,* which is more accurate for this purpose than infant's blood. For a repeat transfusion the red cells in the second unit of donor blood must be compatible with the antibodies in the plasma of the first unit, which may still be in the infant's circulation.

Still unsettled is the importance of antibodies in the plasma of the donor blood, which may react with the cells in the fetal circulation (a "minor" mismatch) to cause hemolysis and further bilirubinemia. Generally, group O Rh-negative blood is used in exchange transfusions for Rh or ABO incompatibility. Because group O blood contains a variable amount of anti-A and anti-B antibodies, it is customary to use blood from donors who have a low titer of these antibodies, in case the infant is group A or B instead of O ("low titer O-negative blood"). Most hospitals keep a fresh unit of such blood on hand. If the infant is group A or B and the mother is of the *same* group, then the problem is resolved by using donor blood which is Rh-negative and of the same blood group. However, if mother and infant are not of the same group in the ABO system, then group O blood is used.

Formerly, the anti-A and anti-B in the donor blood was neutralized by adding Witebsky substance, a porcine A and B antigen. This neutralized anti-A and anti-B of the IgM type but was less effective in neutralizing IgG anti-A and anti-B which could also be present in low titer O, Rh-negative blood. The possible consequences of putting pork antigen into a human are still unknown and the method is seldom used.

Group O Rh-negative cells may be packed, the plasma with most of the anti-A and anti-B antibodies removed, and the cells resuspended in Group AB, Rh-positive plasma. This produces a mixture in which cells as well as plasma are compatible with everything in the infant's circulation under the usual circumstances and is theoretically superior to low titer O Rh-negative blood. It is not yet clear whether it is of practical advantage for diminishing subsequent anemia or hyperbilirubinemia.[7]

---

*In Rh or most other blood group isoimmunization, each successively affected infant is usually more severely diseased, except in ABO isoimmunization, where the reverse is generally true and past maternal history is less useful.

*Infants transferred to another hospital for exchange transfusion should always have a fresh specimen of maternal serum sent with them.

Temperature. The donor blood should be warmed toward neutral (37°C; 98.6°F) before infusion into a newborn infant. The replacement, twice over, of the infant's blood volume with refrigerated donor blood can produce significant hypothermia, and it considerably increases his oxygen requirements during the body's attempt to return to normal temperature. Furthermore, if the catheter tip is near the right atrium, a jet of cold blood could strike the wall of the right atrium and the conduction system of the heart and cause cardiac arrhythmia. Blood can be easily warmed by connecting the tubing from the donor bottle to a coil of plastic tubing (available commercially) and put in a 37°C water bath. Exposure to temperatures greater than 37°C can cause erythrocyte injury and lead to hemolysis.

Hematocrit. Donor blood has a subnormal hematocrit because of dilution by the acid-citrate-dextrose (ACD) anticoagulant. If the bottle or bag is not shaken repeatedly, the blood will settle during the exchange and if the whole unit is used the baby will then receive blood of very low hematocrit toward the end of the exchange and be left anemic. When blood has settled enough so that there is a distinct level separating supernatant plasma from the red cell mass, even the top 1 or 2 cm of cell mass will have a very low hematocrit and reduce that of the baby. The donor blood hematocrit is important not only because of its immediate effects but because the late anemia, which can occur several weeks after exchange transfusion, is most severe in infants who have low hematocrit at the end of the last exchange tranfusion. Caution must be used in manipulation of hematocrit because, in an attempt to avoid or correct anemia, the baby can be made polycythemic, with resultant circulatory embarrassment. The most physiologic hematocrit for extrauterine life is 43 to 45 per cent.

After the blood settles, 50 to 100 ml of plasma can be removed and the remainder used with continuous shaking. It is best to order the blood in a plastic bag with multiple satellite transfer packs, so that the plasma can be removed into one of the satellite packs without entering the unit and risking contamination. Allen and Diamond allow the blood to settle in a bottle that is laid on its side, then withdraw it from the zone midway between top and bottom during the first half of the exchange, after which they turn the bottle gently upright and use the settled cells from the lower side of the bottle.

Chemical composition is another important factor in donor blood. There is more than enough ACD in donor blood to bind all the calcium in the unit; the excess will bind such divalent cations as calcium and magnesium in the baby's circulation. The combined effect of this binding and flushing out by the exchange process lowers the concentration of ionized calcium and magnesium. The degree to which this occurs depends on the rate at which the exchange transfusion is conducted, as well as on the total volume. When the process is slow enough, calcium reserves are mobilized and the serum concentration is maintained at a safe level. Since symptomatic hypocalcemia can occur, a slow periodic infusion of calcium throughout the exchange transfusion is customary.[1] Hypomagnesemia may be a very important factor because of the potent effects of this ion upon the vascular smooth muscle.

Even recently collected ACD-anticoagulated donor blood has a very low pH. The exact chemical composition varies from unit to unit, but three- or four-day-old ACD blood has a mixed metabolic and respiratory acidosis, a pH of 6.7 or less, pCO_2 of 80 or 90 mm or more, and a base deficit of at least 15 mEq per liter. The metabolic component of the acidosis is due to the combined effects of anaerobic metabolism with an accumulation of lactate and the acid citrate of the anticoagulant. When transfused into the circulation of a vigorous full-term newborn infant, the blood is buffered, the excess CO_2 removed by the lungs, and the citrate metabolized. If these compensatory mechanisms are adequate, there is a transient acidosis and, as the citrate is metabolized, the compensated infant may become alkalotic. On the other hand, a premature infant, or one with compromised pulmonary function and metabolic acidosis secondary to hypoxia, will not be able to compensate adequately.[8,16] Since 90 per cent of his circulating blood is being replaced with very acidotic blood, this infant may become more acidotic and deteriorate after exchange transfusions with such blood. If the donor blood is buffered with 30 to 40 ml of 0.3 Molar tris-(hydroxymethyl)-aminomethane (THAM) added to 1 unit of ACD-blood, the pH will be brought to a reasonable range. However, two major precautions must be observed:

1. The blood should not be over-corrected; part

of the THAM is added, the blood mixed, the pH checked and more THAM added as necessary;

2. The buffering should be limited to blood used in those conditions which suggest the infant would not buffer the blood himself, as judged by the general condition, pH, pO_2 and pCO_2 of arterial blood. THAM is superior to sodium bicarbonate for this purpose because it contains much less sodium.

Freshly banked blood is generally used to avoid the higher levels of potassium found in older banked blood. Symptomatic hyperkalemia can occur when donor blood with a very high concentration of potassium is used. The moderate load of potassium in relatively fresh blood (less than a week old) is easily handled by most newborns.

There may be other characteristics of donor blood which have physiological significance, such as the amount of kinins and kininases in banked blood, which could also profoundly affect the infant's circulation.

Heparinized blood, with a higher hematocrit and a higher pH (usually more than 7.1) than ACD blood, does not affect blood calcium or magnesium levels and, because it "heparinizes" the baby, there is less clot formation at the end of the catheter. These advantages are partly offset by the difficulties in obtaining heparinized blood in some localities. It must be ordered ahead of time and used within 48 hours of its collection. When the baby becomes heparinized by an exchange with this type of blood, a counteracting dose of protamine sulfate at the end of the exchange will correct the iatrogenic clotting defect. Since part of the heparin is metabolized during the procedure, enough protamine sulfate can be given to counteract half of the amount of heparin given with the donor blood. At the end of a standard two-volume exchange, about 90 per cent of the infant's blood volume will be composed of donor blood so that the amount of heparin in the baby can be calculated on this basis. Some clinicians prefer not to give protamine sulfate because of its own toxic properties; but the heparin is soon metabolized and usually does not produce significant coagulation problems.

Albumin

Because of the bilirubin-binding properties of albumin, intravenous infusions of salt-poor albumin have been used to increase the removal of bilirubin during exchange transfusions and to prevent bilirubin toxicity in jaundiced infants who might be too ill to tolerate an exchange transfusion.[15] Two grams of salt-poor albumin per kilogram of body weight, given intravenously during the hour preceding a standard exchange transfusion, increases the amount of bilirubin removed up to 50 per cent. The albumin draws the indirect bilirubin and water into the vascular compartment, which increases the efficiency of the exchange. However, one must be certain that the infant can tolerate this expansion of blood volume. It is not yet clear whether this procedure reduces the total number of exchange transfusions required. It may be more useful in infants with low plasma albumin concentration in relation to bilirubin than in those who have more than enough albumin to bind all the available indirect bilirubin.

In newborn infants who have dangerous levels of bilirubin and are too ill to tolerate exchange, or when there is a delay in obtaining donor blood, some clinicians give albumin to prevent bilirubin toxicity. The residual bilirubin binding capacity of the plasma may be used to guide such therapy.[21] Since this technique is not generally available, one might use the serum albumin concentration as a rough guide for giving or repeating the albumin therapy. (It is not uncommon to infuse a dose of 0.5 gm per kg of body weight daily in order to maintain the albumin concentration at the desired level.)*

One objection to infusions of albumin in trying to avoid an exchange has been that, if a great deal of bilirubin is drawn out into the plasma, the bilirubin concentration will rise and can no longer be used as an indication for subsequent exchange transfusion. In our experience, the bilirubin usually rises only 1 or 2 mg per 100 ml while the hematocrit falls 1 or 2 per cent (due to hemodilution). A greater rise in bilirubin concentration would indicate much unbound bilirubin in the tissues and a more severe condition than the pre-treatment bilirubin concentration indicated. It is stronger evidence for an exchange if the bilirubin remains at this higher concentration during the next two to four hours.

Timing of the Exchange Transfusion

There are two conflicting needs in the timing of an exchange transfusion: Removal of antibody-coated red cells before they are hemolyzed, and sufficient time for the newborn infant to complete the appropriate adaptations to extrauterine life

---

*The concentration should be at least half again as much as is required to bind the amount of bilirubin present at pH 7.4, or even more when the infant is acidotic.

(such as adequate lung expansion, correction of immediate postnatal acidosis, beginning closure of the ductus arteriosus).

When lysis of antibody-coated red cells in the circulation occurs, their hemoglobin is converted to bilirubin in a few hours—each gram of hemoglobin in converted into about 33 mg of bilirubin. Hemoglobin within the intact red cells is distributed only within the vascular compartment and is removed easily by an exchange, whereas bilirubin is distributed more widely throughout the body and not so easily removed by exchange transfusion. It seems wise to transfuse at the earliest possible moment any infant who is predicted to need an exchange sooner or later, and thereby reduce the number of subsequent procedures.

On the other hand, provided such infants are not hydropic or severely anemic, there is no clear-cut evidence that a delay until the infant is a few hours of age will increase the need for subsequent exchange. A possible explanation for this is that, while 90 per cent of the red cells in the circulation are removed by a two-volume exchange, excess maternal anti-erythrocyte antibodies are distributed more widely throughout the body and a large fraction will remain in the infant after the exchange and coat new red cells released into the circulation from the infant's bone marrow. Thus, the added hemolysis during a two to four hour delay is an insignificant proportion of the continuing hemolysis.

Assessment of the Infant

As was stated previously, the management of each infant should be highly individualized on the basis of a thorough evaluation of physiological factors, not only the infant's hemoglobin and bilirubin concentration. The measurement of serum albumin, blood glucose and arterial or arterialized capillary blood pH, pO_2 and pCO_2 will be a better guide to management. When there are metabolic factors which enhance bilirubin toxicity, corrective therapy (such as alkali therapy for metabolic acidosis) should be begun promptly.

The infant's general condition should also be considered in choosing the environment in which the procedure is done. Sterile technique is very important, but it is not necessary to use a cold surgical amphitheater with a staff not familiar either with the procedure or with the care of newborn infants to achieve asepsis. A sick infant is much safer in an incubator or, better still, under a radiant warming unit with an oxygen mask or hood as needed and with experienced nurses in attendance.

Mechanics of the Exchange Transfusion

Catheter placement and measurement of venous pressure. The standard exchange transfusion is made through a saline-filled polyethylene catheter inserted into the umbilical vein, as described by Allen and Diamond.[1] It is important to know the position of the tip of this catheter: From the umbilical vein it enters the portal sinus within the liver. An attempt to advance it may cause it to go through the ductus venosus into the inferior vena cava about 75 per cent of the time. It occasionally turns caudally in the vena cava, but generally cephalad. If advanced far enough (about 10 to 12 cm in a full-term newborn) it will reach the right atrium. Alternately, it may not go through the ductus venosus but coil itself within the portal sinus, go off into one of the hepatic radicals or back into the portal vein.

The location is important for measuring venous pressure, assessing cardiac failure and withdrawing and injecting blood. If the catheter does *not* go through the ductus venosus, the portal venous pressure (normal about 9.9 cm of water) and not the central venous pressure will be measured. Portal is higher than central venous pressure by a variable amount, and it may be elevated due to a local phenomenon without concomitant elevation of central venous pressure.

Once through the ductus venosus and into the inferior vena cava, an accurate measurement of venous pressure can be made (normal 1.4 cm of water [SD±2.0 cm]). As the catheter is advanced, the location can be determined by the variations in pressure with respirations. In the portal sinus, the swings with respiration are small (generally only 2.4 cm of water), the pressure rising on inspiration and falling on expiration. As it goes through the ductus and into the inferior vena cava the changes are greater (5 to 13 cm of water) but still rising on inspiration.[4] When the catheter tip is above the diaphragm and in the thorax, the pressure falls with the start of each inspiration. It is not necessary to leave the catheter tip above the diaphragm—it can be pulled back just below it, with the assurance that it is in the inferior vena cava and that pressure measurements can be trusted. Since an abnormal central venous pressure has serious therapeutic implications, errors in measurement must be avoided by appropriate attention to these details.

The proper position for the catheter tip during an exchange is not known. Most workers agree that it should not be in the right atrium, where a jet of donor blood unmixed with the infant's venous blood may hit the heart wall. Injecting and withdrawing blood from the portal sinus has the disadvantage of distending and contracting a structure of limited capacity. The inferior vena cava has a large volume of blood flow, particularly above the level at which the hepatic vein joins it. The usual amount of blood removed or injected here is only a small portion of the total flow, the hemodynamic effect is less and there is some mixing by the time the blood reaches the heart.

The exchange transfusion itself is a simple flushing out of the intravascular space. The blood does not flow steadily in and out of the baby but is removed and replaced in increments of 10 to 20 ml. The first syringefull (increment) removed is only the baby's blood but, as the procedure goes on, more of the blood removed with each cycle is donor blood infused during the earlier cycles. From this has come the erroneous belief that the use of larger increments would give a more efficient exchange for any given total volume exchanged. Dangerously large volumes of blood are thus sometimes removed in each increment in the mistaken belief that more bilirubin is being washed out. This is true theoretically but of no practical consequence.[18] As an illustration, consider a one-volume exchange transfusion in a newborn infant with a blood volume of 300 ml. If the entire blood volume could be removed in one increment and then replaced with donor blood, the *vascular compartment* (but not the extracellular fluid space) would have been flushed out with an efficiency of 100 per cent. If half the blood volume (150 ml) is removed at once (still an unthinkably large amount) and replaced, then 150 ml removed again and replaced, the efficiency would be only 75 per cent. As the ratio of the increment volume to the infant's blood volume gets smaller, the efficiency decreases toward a minimum value of 63 per cent—the same efficiency as one would get with steady flow through the baby. Within the range of practicality, there is nothing to be gained by using a larger volume: For example, the efficiency of an exchange transfusion using 30 ml increments is insignificantly greater than one using 5 ml increments.

The potential disadvantage of larger increments is the stress put upon the infant's cardiovascular adaptive mechanisms by repeatedly removing and reinfusing one-fifteenth to one-tenth of his total blood volume.[23]

The lower limit of the increment to be used is set by the dead space of the catheter and stopcock which connects the syringe to the infant's circulation. The blood in this dead space is not really exchanged. At the end of the "in" phase of each cycle, donor blood is left in the dead space; with the next "out" phase, this unmixed donor blood comes into the syringe before any of the baby's blood is removed. Not until the dead space equals one-tenth the volume removed in the syringe does this significantly affect the efficiency of the process. This problem can be managed either by using a narrower catheter with a smaller volume or by flushing the catheter at the end of each "in" phase by drawing back twice the volume of the dead space and reinfusing it.

Since the usual exchange with 10 to 20 ml increments is no more efficient than a steady flow of blood into and out of the infant, this latter method has been used without producing any change in the blood volume. Valentine[19] has heparinized the infant and withdrawn the blood from the umbilical vein at the same rate as it was infused into the saphenous. This can also be done through a double lumen catheter via the umbilical vein. An indwelling catheter is often placed in the umbilical artery of a sick infant for serial determinations of blood gases. If such an infant needs an exchange transfusion, a second catheter in the umbilical vein will permit a continuous exchange into the venous catheter and out the arterial.

The efficiency with the usual exchange transfusion technique is shown in the following tabulation:

Volume of Blood Used (Per Cent of Baby's Blood Volume)	*Per Cent of Baby's Original Blood Replaced by Donor Blood*
0.5	40
1.0	65
2.0	85
3.0	95

The original hematocrit and that of donor blood can help to predict the baby's hematocrit at the end of an exchange procedure of a given volume. Only a small exchange with sedimented or packed red cells is needed to correct a low hematocrit rapidly. Continuing the exchange beyond twice the infant's blood volume will do little to remove antibody-coated red cells.

These figures on the efficiency of the exchange are for the washout of the vascular compartment only, and do not apply to the removal of bilirubin.[3,18] At the end of the standard two-volume exchange the concentration of bilirubin will still be approximately half that at the start, yet the bilirubin removed and in the exhaust bucket will be twice the amount circulating in the plasma at the start (Chart 2). Obviously, a great deal of bilirubin must have entered the circulation during the course of the exchange.

Bilirubin equilibration. Indirect bilirubin behaves as though it is distributed into three spaces[18]: The circulating plasma and two extravascular compartments—one of which equilibrates very rapidly with the circulating plasma (presumably extravascular-extracellular fluid) and the other (intracellular?) which equilibrates very slowly with the other two spaces. The first two are in such close communication that they are, in effect, one. As soon as the concentration in the plasma falls even slightly, bilirubin moves from the extracellular fluid into the plasma until equilibrium is reached. As to bilirubin removal, the exchange transfusion flushes out a much larger space than just the vascular compartment.[3,18] In order to move bilirubin from the slowly equilibrating pool into the extracellular fluid and plasma, a high concentration gradient and a long time is required. Such a gradient is not established until later in the exchange transfusion when a large amount of bilirubin has been washed out of the plasma and other extracellular fluid. Since the albumin in the donor blood is not saturated with bilirubin, it, too, contributes to the movement of bilirubin into the vascular space.

This slower equilibration process contributes to the post-exchange rise (rebound) in bilirubin concentration in the four hours after the procedure has ended. So little of this bilirubin moves into the plasma during a standard exchange transfusion that there is no great advantage in a slower one in the hope of removing more bilirubin as this equilibration occurs, unless one is willing to prolong the procedure at least another one or two hours. Valentine[19] uses his continuous exchange technique to do very slow exchanges (four hours or more) to permit this equilibration to occur and more bilirubin to be removed.

The amount of bilirubin removed at any point in the course of an exchange transfusion depends upon the concentration of bilirubin in the plasma at that point. As the bilirubin concentration falls, so does the amount removed; therefore, two separate two-volume exchanges can remove more bilirubin than one four-volume exchange. Generally, after one two-volume exchange, the plasma bilirubin concentration is low enough that it is wiser to wait four hours before considering another exchange. Occasionally, however, the initial bilirubin is so high or the hemolytic process so severe that additional bilirubin is produced during the time of the exchange, and the concentration is still high at the end of a standard exchange transfusion. A great deal more bilirubin, therefore, can be removed by extending the procedure to an exchange of three or even four times the baby's blood volume. Although even more bilirubin would

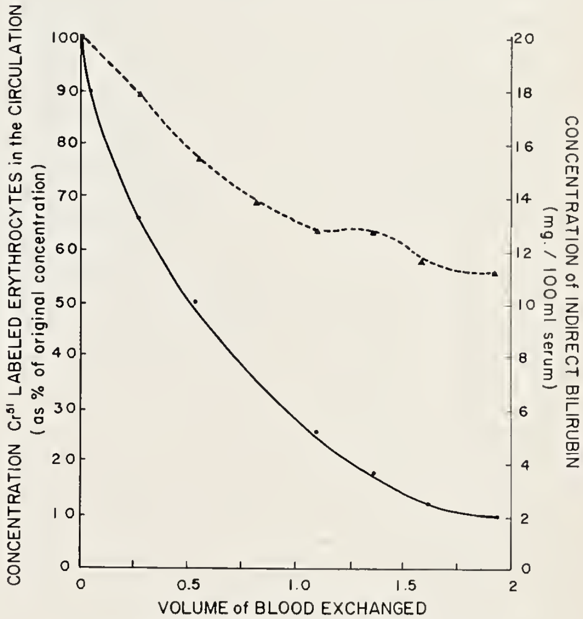


Chart 2.—The efficiency of an exchange transfusion in a 2,865 gm newborn. Cr^{51}-labeled red cells had previously been infused into the infant's circulation; the fall in their concentration (solid line) during the exchange transfusion is a measure of the efficiency with which the vascular compartment is washed out. Note that the fall in indirect bilirubin concentration (dotted line) is not as great. The difference between the two lines is due to the indirect bilirubin which has moved from extravascular areas into the vascular compartment during the procedure. The baby had a total of 33.2 mg of indirect bilirubin in his intravascular compartment at the start of the exchange. A total of 43.9 mg of indirect bilirubin was removed by the procedure, yet the serum concentration was only halved, and 18.9 mg remained in his vascular space at the end, so that 29.6 mg moved into the vascular space during the exchange. (Graph derived from the data of Sproul and Smith.[18])

be removed by waiting four hours before the next exchange, the bilirubin would climb to very dangerous levels. Chart 3 illustrates such an exceptional case, which indicates that occasionally there is a place for larger exchanges.

Post-Exchange Tranfusion Management

The principles of management of any exchange after the first one are implicit in the preceding discussion. Hematocrit or hemoglobin must be remeasured, all the critical variables should be reevaluated serially, and the first bilirubin measured three to four hours after the exchange when the rebound due to re-equilibration is over. This measurement should not be postponed, no matter how certain that another exchange will not be needed. Platelets should also be evaluated by peripheral smear, and by count if they appear low. A moderate transient thrombocytopenia commonly occurs after an exchange transfusion; however, in infants with severe hemolytic disease, thrombocytopenia may be severe and prolonged and require treatment with very fresh blood or platelet transfusions. Depletion of other clotting factors by exchange transfusion has yet to be evaluated.

The incidence of positive blood cultures at the end of exchange has been high enough that many clinicians give antibiotics afterward. The need for such therapy undoubtedly varies inversely with the quality of sterile technique during the procedure.

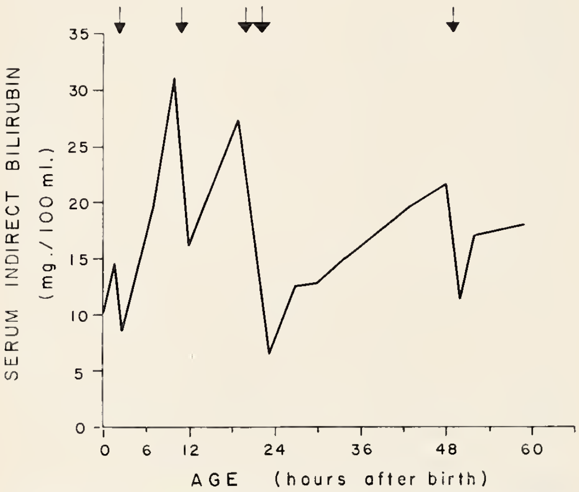


Chart 3.—↓=Standard "two-volume" exchange transfusion. ↓↓="four-volume" exchange transfusion.

Course of severe Rh hemolytic disease in a full-term newborn. The rapidly rising bilirubin after the first exchange was a clue that a four-volume exchange might be needed. The second two-volume exchange halved the bilirubin concentration but, since it was 17 mg per 100 ml at the end, continuing the exchange would have removed much more bilirubin. The four-volume exchange reduced bilirubin to one-fourth the pre-exchange level, and the post-exchange rise was much slower.

Note delay in repeat exchanges due to failure to anticipate the need for several units of donor blood.

There are definite hazards and no particular advantages in leaving the catheter in the umbilical vein for a prolonged period after the exchange. Usually, the vein can be reentered easily if another exchange is needed. If necessary, one can cut down on the umbilical vein, which runs longitudinally just under the skin, by a transverse incision about 1 cm cephalad of the umbilical stump.

Finally, when an infant with hemolytic disease is discharged from the nursery, one must not forget the late anemia (see section: Donor Blood) which is most severe at one to two months of age and may require a simple transfusion.

REFERENCES

1. Allen, F. H., Jr., and Diamond, L. K.: Erythroblastosis Fetalis, including Exchange Transfusion Technic. Little Brown & Co., Boston, 1958, and New Engl. J. Med., 257:659-668, 705-712, and 761-772, 1957.

2. American Academy of Pediatrics: Committee on Fetus and Newborn: Recommendations on a uniform bilirubin standard, Pediatrics, 31:878-890, 1963.

3. Brown, A. K., and Zuelzer, W. W.: Studies in hyperbilirubinemia. 1. Hyperbilirubinemia of the newborn unrelated to isoimmunization; II (with A. R. Robinson) Clearance of bilirubin from plasma and extravascular space in newborn infants during exchange transfusion, Am. J. Dis. Child., 93:263-286, 1957.

4. Cottom, D. G., and Young, M.: Venous pressure measurement in exchange transfusion, Arch. Dis. Child., 40:323-325, 1965.

5. Diamond, I., and Schmid, R.: Experimental bilirubin encephalopathy. The mode of entry of bilirubin-^{14}C into the central nervous system, J. Clin. Invest., 45:678-689, 1966.

6. Freda, V. J., Gorman, J. G., and Pollack, W.: Rh factor: Prevention of isoimmunization and clinical trial on mothers, Science, 151:828-829, 1966.

7. Goldfarb, D. L., Ginsberg, V., Kaufman, M., Robinson, M. G., and Watson, R. J.: Hemolytic disease of the newborn due to ABO incompatibility. A study of the use of Group O erythrocytes in AB plasma, Pediatrics, 34: 664-669, 1964.

8. Lenoski, E. F., and Hodgman, J. E.: Acid-base homeostasis during exchange transfusion, paper #63, 12th Annual Meeting, Western Society for Pediatric Research, Salt Lake City, 17 November 1964.

9. Liley, A. W.: Errors in the assessment of hemolytic disease from amniotic fluid, Am. J. Ob. & Gyn., 86:485-494, 1963.

10. Liley, A. W.: Intrauterine transfusion of foetus in haemolytic disease, Brit. M. J., 2:1107-1109, 1963.

11. Liley, A. W.: Use of amniocentesis and fetal transfusion in erythroblastosis fetalis, Pediatrics, 35:836-847, 1965.

12. McKay, R. J., Jr.: Current status of use of exchange transfusion in newborn infants, Pediatrics, 33: 763-767, 1964.

13. Odell, G. B.: Distribution of bilirubin between albumin and mitochondria, J. Pediat., 68:164-180, 1966.

14. Odell, G. B.: Factors influencing the binding of bilirubin by albumin, in Kernicterus, A. Sass-Kortsák, ed., Toronto, Univ. Toronto Press, 1961, pp. 199-207.

15. Odell, G. B., Cohen, S. N., and Gordes, E. H.: Administration of albumin in the management of hyperbilirubinemia by exchange transfusions, Pediatrics, 30: 613-621, 1962.

16. Oliver, Jr., T. K.: The use of THAM-buffered ACD blood in high risk infants who require exchange transfusion (abstract), J. Pediat., 67:951, 1965.

17. Porter, E. G., and Waters, W. J.: A rapid micromethod for measuring the reserve albumin binding capacity in serum from newborn infants with hyperbilirubinemia, J. Lab. & Clin. Med., 67:660-668, 1966.

18. Sproul, A., and Smith, L.: Bilirubin equilibration during exchange transfusion in hemolytic disease of the newborn, J. Pediat., 65:12-26, 1964.

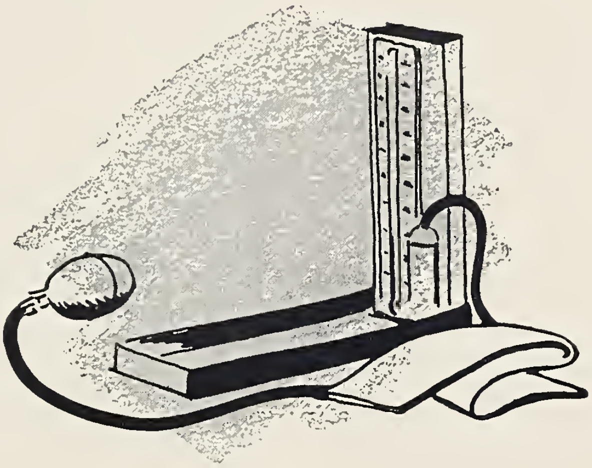
19. Valentine, G. H.: Exchange transfusion by continuous drip using heparinized blood, Lancet, 1:10, 1962.

20. Waters, W. J.: The protective action of albumin in bilirubin toxicity in newborn puppies, in Kernicterus, A. Sass-Kortsák, ed., Toronto, Univ. Toronto Press, 1961, pp. 219-221.

21. Waters, W. J., and Potter, E. G.: The reserve albumin binding capacity as a criterion for exchange transfusion (and discussion by Odell, G. B.), J. Pediat., 67: 1042-1044, 1965.

22. Wishinggrad, L., Cornblath, M., Takakuwa, T., Rozenfeld, I. M., Elegant, L. B., Kaufman, A., Lassers, E., and Klein, R. I.: Studies of non-hemolytic hyperbilirubinemia in premature infants, 1. Prospective randomized selection for exchange transfusion with observations on the levels of serum bilirubin with and without exchange transfusion and neurologic evaluations one year after birth, Pediatrics, 36:162-172, 1965.

23. Young, M., and Cottom, D.: Arterial and venous blood pressure response during a reduction in blood volume and hypoxia and hypercapnia in infants during the first two days of life, Pediatrics, 37:733-742, 1966.



CASE REPORTS

Congenital Toxoplasmosis With Hemolytic Anemia

LESLIE G. NELSON, M.D., AND
JOAN E. HODGMAN, M.D., *Los Angeles*

AN INFANT WITH congenital toxoplasmosis of the visceral type, who had hepatosplenomegaly and jaundice when first examined, was cared for at the Premature Center of the Los Angeles County Hospital. The infant had an isolated episode of acute hemolytic anemia, which is an unusual finding in this disease.

Case Report

The patient was born of a 26-year-old gravida 4 para 3 Mexican-American woman following 36 weeks of gestation. The mother had no prenatal care and had taken no medicines during this pregnancy. The only illness was a "bad cold" of four days' duration at five months of gestation. No fever, rash or lymphadenopathy was recalled during this illness. At the time of the mother's illness, the patient's father, age 28 years, was also ill with high fever and malaise. He made an uneventful recovery and had no medical care. The three normal siblings aged five, four, and three years were not ill at that time.

The delivery of this infant, a girl, was in a physician's office after a spontaneous labor. The amniotic fluid was described as "foul smelling." The infant was admitted first to another hospital and was transferred to the Premature Center of the Los Angeles County Hospital at two days of age.

On admission the infant weighed 1,960 gm. She had both jaundice and hepatosplenomegaly. Hemoglobin content was of 18 gm per 100 ml of blood, and urinalysis was within normal limits. The total bilirubin concentration was 9.6 mg per 100 ml and the serologic test for syphilis (VDRL) was negative. An x-ray film of the chest showed no abnormality but enlargement of the liver and spleen was apparent on a radiograph of the abdomen. A blood culture showed no growth. No cytomegalic inclusion cells were found in the urine on repeated examination.

Bilirubin levels during the following 20 days are shown in Table 1. These showed persistent high levels of the direct-reacting bilirubin fraction. At 20 days of age, liver function tests included albumin of 4.0 gm and globulin of 2.9 gm per 100 ml and a serum glutamicoxaloacetic transaminase of 225 units. The hemoglobin level at that time was 9.9 gm per 100 ml.

Both the patient's and the mother's blood types

TABLE 1.—*Serial Bilirubin Determinations in Infant with Congenital Toxoplasmosis*

	Bilirubin (mg per cent)	
Age (days)	*Total*	*Direct*
2	9.6	....
3	9.0	4.6
4	8.0	4.2
20	5.2	2.6
22	5.1	2.8

From the Department of Pediatrics, University of Southern California, School of Medicine and the Los Angeles County Hospital.

Supported in part by a grant from the John A. Hartford Foundation.

Submitted 12 April 1966.

Reprint requests to: Department of Pediatrics, Los Angeles County General Hospital, 1200 North State Street, Los Angeles 90033 (Dr. Hodgman).

were group A, Rh positive. Reaction to a Coombs test on the patient's blood was negative. Seven days later the hemoglobin had dropped to 6.8 gm per 100 ml, the packed cell volume was 20 per cent, and the total leukocyte count was 4,500 per cu mm with a normal differential. The platelets appeared slightly reduced in number on a peripheral smear. Two normoblasts were seen per 100 leukocytes. The reticulocyte count was 3.4 per cent when corrected for anemia. The erythrocytes were normochromic and the mean corpuscular hemoglobin concentration was 34 per cent. Microcytes and some spherocytes were present. A sickle cell preparation was negative. An erythrocyte glucose-6-phosphate dehydrogenase spot test was within normal limits.

A transfusion of 20 ml of sedimented red blood cells was given on the twenty-seventh day. Active erythropoesis was seen on bone marrow aspiration at 37 days of age. The myeloid series was within normal limits and no abnormal cells were seen. A percutaneous liver biopsy done at 32 days of age showed extramedullary hematopoesis with conspicuous hemosiderosis consistent with a hemolytic process. After the transfusion and until the time of discharge, the hemoglobin level stabilized between 8.5 and 9.6 gm per 100 ml.

At 20 days of age, no red or light reflex could be elicited in the right eye. The cornea was clear, the pupil did not dilate well, and posterior synechiae were present. The fundus could not be seen adequately. The left cornea was clear and the pupil dilated well. The fundus was easily visualized and no abnormalities were present.

In the nursery the baby was vigorous and had regained her admission weight by the tenth day. She was asymptomatic during her entire stay in hospital. No therapy other than a routine multiple vitamin preparation was given in the nursery. The infant was discharged from the hospital at 46 days of age weighing 2,850 gm and with equivocal clinical jaundice and persistent hepatosplenomegaly.

She was observed in the outpatient department until twenty-two and a half months of age. Weight gain was from 4,252 gm at five months to 8,796 gm at 11 months (both in the twenty-fifth percentile).[16] Head circumference at 11 months was 43 cm (third percentile).[16] At five months of age hepatosplenomegaly was present without jaundice. A Sabin-Feldman dye test was positive at 1:64,000 (Table 2). X-ray films of the skull showed no abnormality. Ophthalmoscopic examination after sedation indicated both micro-opthalmia and iritis of the right eye. Again the fundus could not be visualized. Both vitreous haze and chorioretinitis were present in the left eye. Internal strabismus of the right eye and wandering eye motions had developed by 11 months of age and persisted thereafter.

TABLE 2.—*Sabin-Feldman Dye Titers in a Case of Congenital Toxoplasmosis*

Age (months)	*Patient*	*Mother*
5	1:64,000	1:64,000
11	1:32,000	1:64,000
22	1:16,000	1:64,000

The hemoglobin rose from 9.0 gm per 100 ml at five months of age to 12.2 gm at 11 months. Results of the repeated Sabin-Feldman dye tests and complement fixation tests for toxoplasmosis for both the patient and her mother are tabulated in Table 2. At 11 months of age, pyrimethamine, 12.5 mg per day and sulfisoxasole 150 mg per kg of body weight per day, were begun and continued for 30 days with no change in the patient's condition.

Gesell developmental testing done at the chronological age of twenty-two and a half months gave the following results: Motor 17 to 18 months, adaptive 16 months, language 15 months, and social-personal 15 to 16 months. Despite the obvious visual difficulties, she was able to secure the pellet against a white background, establishing that poor vision was not the only cause for her delayed development. Her adaptive behavior at a 16-month level would seem to be the most accurate appraisal of her development at this time.*

The mother was admitted to hospital seven months after birth of the patient for an incomplete abortion. Curettement of the uterus was performed, and on examination of the tissue removed at curettage no toxoplasma was observed.

Discussion

Since the recognition of the first cases of congenital toxoplasmosis published in 1939,[18] a concept has persisted that the disease presents as a parasitic central nervous system infection with hydrocephalus or microcephalus, convulsions, intracerebral calcification, chorioretinitis and mental retardation. In one of the early reports, the symptoms first observed were referable to the viscera.[8] In 1956, Eichenwald[9] reported a series of 156 cases of congenital toxoplasmosis. One hundred and eight of the patients had central nervous system abnormalities whereas 44 patients had predominately visceral findings. In the latter group, jaundice was present in 79 per cent of cases, anemia in 77 per cent, chorioretinitis in 66 per cent and splenomegaly in 90 per cent. Intracranial calcifications were found in only 4.5 per cent of this group, and hydrocephalus in none. Couvreur and Desmonts,[7] in a series of 300 cases of congenital toxoplasmosis reported from France, found neurological disorders in 51 per cent, hydrocephaly or microcephaly in 26 per cent, ocular disorders in 76 per cent, intracranial calcifications in 33 per cent, jaundice in 20 per cent and hepatosplenomegaly in 18 per cent. Other smaller series have shown a preponderance of patients with central nervous system disease and a smaller proportion with visceral manifestations.[1,4,6,15] In cases of congenital toxoplasmosis in which the early symptoms were related primarily to visceral infections, the central nervous system was ultimately affected to a greater or lesser degree.[9]

---

*Developmental testing done by Anabel Teberg, M.D., assistant clinical professor of pediatrics, University of Southern California.

Jaundice is common in the visceral form of the disease, but examples of well documented cases of elevated direct-reading bilirubin are uncommon in the literature.[5] Cowen and coworkers[8] described a case of congenital toxoplasmosis in which total bilirubin when the patient was nine days old was 15.3 mg per 100 ml, of which 8.5 mg per 100 ml was direct reacting. At 30 days of age the same infant had total bilirubin of 5.8 mg per 100 ml with a direct bilirubin of 3.7 mg per 100 ml. Another patient had well documented direct hyperbilirubinemia of 12 mg per 100 ml on the first day of life. Elevated direct bilirubin has been reported in only two additional cases.[15,19] A direct bilirubin level over 1 mg per 100 ml is an unusual finding in the newborn,[12] and when it is increased, congenital toxoplasmosis should be considered in differential diagnosis.

Several cases have been reported in which infants at birth who died of anemia resembling hemolytic disease of the newborn, were found at necropsy to have congenital toxoplasmosis with no apparent blood incompatibility.[2,3,5] Few cases have been reported in which infants who had anemia with congenital toxoplasmosis survived.[8,11,19] The case herein reported, in which anemia was noted when the infant was 27 days old, is a well documented instance of hemolysis which must be considered as a part of the visceral manifestations of congenital toxoplasmosis.

The benefit of treatment in congenital toxoplasmosis is questionable. Although both sulfonamides and pyrimethamine are active against toxoplasma *in vitro,* the results *in vivo* have been equivocal.[20] Eichenwald found that in a small group of infants treatment appeared to shorten the acute phase of the illness, and reversion of dye test titers to lower levels also occurred. Treatment does not appear to prevent the neurologic sequelae of neonatal infection.

The prognosis in congenital toxoplasmosis remains poor. The mortality in a group of 103 cases reported by Feldman[10] was 27 per cent in premature infants and 12 per cent in term infants. In Eichenwald's[9] study of 156 cases the overall mortality was 12 per cent. Of the surviving infants, 90 per cent had mental retardation, 70 per cent had convulsions, spasticity or other neurologic abnormalities and 50 per cent had severely impaired vision. Chorioretinitis may not be present at birth, particularly in the visceral group, but it may develop, as in the present case, from two weeks to six months later.[7,13,17]

Summary

Congenital toxoplasmosis in a premature infant first came to attention because of visceral manifestations of jaundice and hepatosplenomegaly at two days of age. Direct hyperbilirubinemia persisted for 46 days and an isolated episode of acute hemolytic anemia occurred at 27 days of age. Ocular changes were first noted at 20 days of age. The diagnosis was confirmed by demonstrating persistently elevated Sabin-Feldman dye test titers in both mother and infant.

At twenty-two and a half months of age the infant was growing normally but with severe visual impairment and developmental retardation.

REFERENCES

1. Adams, F. H., Adams, J. M., Kabler, P., and Cooney, M.: Toxoplasmosis in children, Pediatrics, 2:511-519, 1948.

2. Alexander, C. M., and Callister, J. W.: Toxoplasmosis of newborn (histologic changes in mother's lymph node with presumptive isolation of toxoplasma from mother's lymph node by mouse passage), Arch. Path., 60:563-574, 1955.

3. Bain, A. D., Bowie, J. H., Flint, W. F., Beverley, J. K. A., and Beattie, C. P.: Congenital toxoplasmosis simulating hemolytic disease of the newborn, J. Obstet. Gynec. Brit. Emp., 63:826-832, 1956.

4. Beckett, R. S., and Flynn, F. J.: Toxoplasmosis, report of two new cases, with a classification and with

a demonstration of the organism in the human placenta, New Engl. J. Med., 249:345-350, 1953.

5. Callahan, W. P., Russell, W. O., and Smith, M. G.: Human toxoplasmosis. A clinicopathologic study with presentation of five cases and review of the literature, Medicine, 25:343-397, 1946.

6. Clinical Pathological Conference, J. Pediat., 49:752-764, 1956.

7. Couvreur, J., and Desmonts, G.: Congenital and maternal toxoplasmosis. A review of 300 congenital cases, Deuel Med. Child Neurol., 4:519-530, 1962.

8. Cowen, D., Wolf, A., and Paige, B. H.: Toxoplasmic encephalomyelitis. VI. Clinical diagnosis of infantile or congenital toxoplasmosis: Survival beyond infancy, Arch. Neurol. & Psych., 48:689-739, 1942.

9. Eichenwald, H. F.: A study of congenital toxoplasmosis with particular emphasis on clinical manifestations, sequellae and therapy, in Human Toxoplasmosis, ed. J. Chr. Siim, Williams and Wilkins, Co., Baltimore, 1959, pp. 41-49.

10. Feldman, H. A.: Congenital toxoplasmosis—A study of 103 cases, Amer. J. Dis. Child, 86:487-489, 1953.

11. Gard, S., Magnusson, J. H., and Hagberg, E.: Congenital toxoplasmosis, Acta Pediatrica, 41:15-31.

12. Hodgman, J. E., Nelson, L. G., and Cleland, R. S.: Unpublished data.

13. Hogan, M. J.: Ocular toxoplasmosis, Amer. J. Ophthal., 46:467-494, 1958.

14. Magnusson, J. H., and Wahlgren, F.: Human toxoplasmosis. An account of 12 cases in Sweden, Acta Path. Microbiol, Scand., 25:215-236, 1948.

15. Nathan, A., and Matheson, A.: Toxoplasmosis in infants, report of two cases, J. Pediat., 47:640-644, 1955.

16. Nelson, W. E.: Textbook of Pediatrics, 8th ed., W. B. Saunders Co., Philadelphia, 1964, pp. 48-57.

17. Warren, J., and Sabin, A. B.: Effects of certain antiprotozal drugs on toxoplasma in vitro and in vivo, Proc. Soc. Exp. Biol. Med., 51:15-18, 1942.

18. Wolf, A., Cowen, D., and Paige, B. H.: Toxoplasmic encephalomyelitis. III. A new case of granulomatous encephalomyelitis due to a protozoan, Amer. J. Path., 15:657-694, 1939.

19. Zuelzer, W. W.: Infantile toxoplasmosis—With a report of three new cases, including two in which the patients were identical twins, Arch. Path., 38:1-19, 1944.

Necrotic Arachnidism

MARTIN I. LEWIS, M.D., AND
JAMES F. REGAN, M.D., PH.D., *Los Angeles*

NOT OFTEN DO humans die of spider bite, but a more frequent if less appreciated consequence is cutaneous necrosis at the site of venom injections. The lesions are so fulminant and ugly-appearing that it is difficult to associate them with anything as small as a spider and they are therefore often mistakenly attributed to other causes.

As a case in point, a patient was admitted to our service with extensive necrotic ulcerations on the foot and buttocks. The history was highly suggestive of an insect bite, but there was no known organism in California that was reported capable of producing so astounding a lesion. However, careful review of medical and zoological literature elicited reports of an arachnid, the *Loxosceles spider*—only endemic in certain midwestern states—whose bite did cause necrotic lesions. There was a most remarkable similarity between history and clinical manifestations in the present case and the necrotic arachnidism reported caused by this midwestern species.

Etiology and Epidemiology

Necrotic arachnidism (cutaneous necrosis following spider bite) has been known to physicians of South America for many years. Although Prada in 1896 reported the first case of gangrenocutaneous arachnidism in South America resulting from the bite of a small brown spider, it was not until 1937 that Macchiaviello identified the spider *Loxosceles laeta* as the causative agent of Chilean cutaneous arachnidism—"gangrenous spot." Numerous papers, especially from the University of Chile, have subsequently reported upon the incidence of necrotic arachnidism and on its treatment.

In the United States, reports of identical or very similar cases of necrotic arachnidism (caused by some unknown insect or spider) have frequently appeared in the literature. These date back to as early as 1890, when an article appearing in a local journal of medicine in Missouri reported a case of necrotic arachnidism resulting from the bite of a small spider, the species not known.

Until less than a decade ago, *Lactrodectus mactans* (the Black Widow spider) was the only culprit within the United States known to cause necrotic arachnidism. Then, in 1957, the Missouri Brown spider, *Loxosceles reclusa*,[1] was proved to be capable of causing such lesions. Clinically, the lesion produced by the bite of this spider is one of central necrosis—completely unlike that produced by the black widow, which rarely causes necrosis, but similar to the necrotic, cutaneous ulcerations produced by its South American relative, *Loxosceles laeta*.

Interestingly, the geographic incidence of the

From Queen of Angels Hospital.

Submitted 31 March 1966

Reprint requests to: 947 West 8th Street, Los Angeles 90026 (Dr. Lewis).

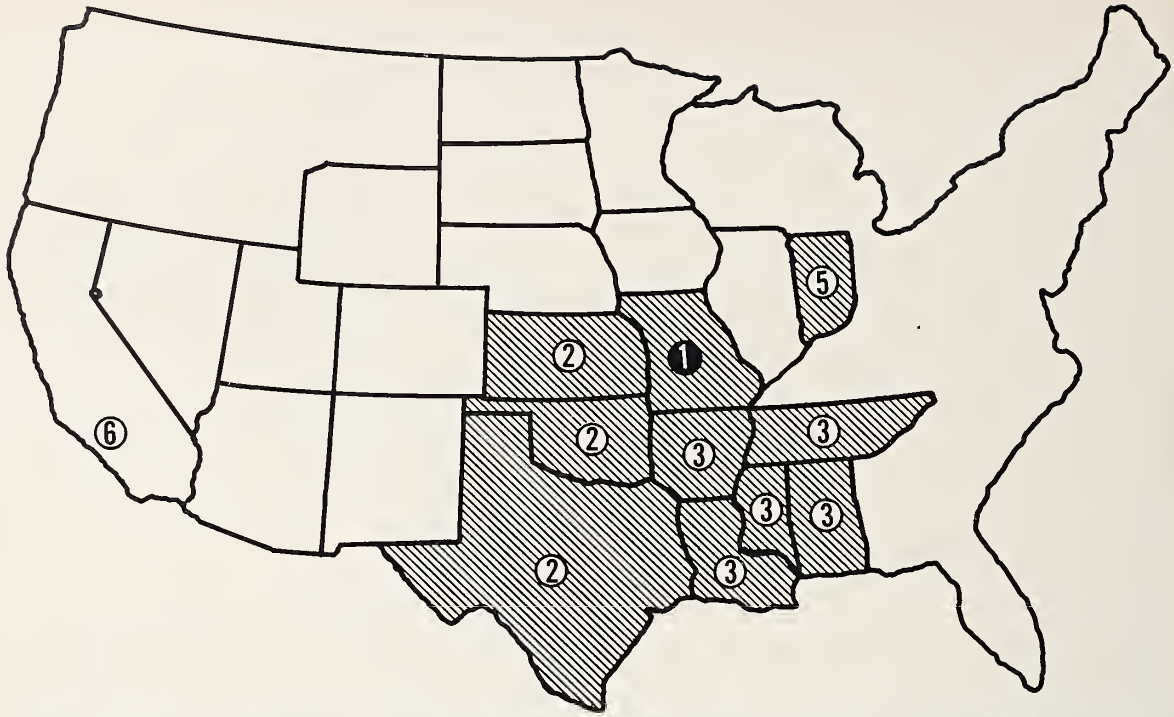


Figure 1.—Known distribution of *Loxosceles reclusa* in the United States. (1) First reported case of necrotic arachnidism—Missouri, 1957.[11] (2) By August 1962 cases of necrotic arachnidism had been reported in Kansas, Texas and Oklahoma. (3) Louisiana, Arkansas, Tennessee, Alabama and Mississippi reported the presence of the spider *L. reclusa* by 1962. (5) Reported case of necrotic arachnidism, Indiana, 1964. (6) Case report in this paper.

necrotic arachnidism caused by *L. reclusa* does not coincide with the reported distribution of the spider (Figure 1). Although in the literature up to 1962 reports of such lesions had been limited to Kansas, Missouri, Oklahoma and Texas, the prevalence of the spider had been recorded in a larger area, including Alabama, Arkansas, Louisiana, Mississippi and Tennessee.[5] Not one case of necrotic arachnidism from these latter five states has been reported. By 1964 an authenticated case of necrotic arachnidism had been reported as far north as Indiana.[9]

In Los Angeles, within the past year, two cases of severe necrotic arachnidism resulting from the bite of a small spider were recorded but were not reported in the medical literature. The lesion produced in both cases was similar to that resulting from the bite of the Missouri Brown spider.

Related to the exotic occurrence of necrotic arachnidism on the west coast, two other species of *Loxosceles*—*L. unicolor* and *L. arizonica*—are known to be endemic to Southern California. It well may be that the cases of necrotic arachnidism reported were due to *Loxosceles unicolor, Keyserling,* which has a distribution covering ". . . Western United States, from New Mexico and Utah to California, southward into adjacent Mexico, at least to Southern Sonora and Baja California and eastward into New Mexico and Texas . . ." (Gertsch,[4] 1958).

A second possibility is that the other, natural

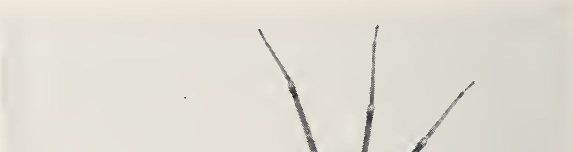


Figure 2.—*Loxosceles reclusa*, female, supplied by Dr. C. W. Wingo, University of Missouri. The body is about 9 mm long.

inhabitant of Southern California, *L. arizonica*, may also be capable of causing necrotic arachnidism. At present, however, neither *L. unicolor K.* nor *L. arizonica* has definitely been implicated. A third possibility is that *Loxosceles reclusa* (the Missouri Brown spider) or two other species (*Loxosceles rufescens* and *Loxosceles devia*) have been transported into the Southern California area.

It must be emphasized that, of the more than 20 species of *Loxosceles* indigenous to the United States, only *L. reclusa* has definitely been identified (by Wingo and coworkers, at the University of Missouri) with necrotic arachnidism in this country. Further, there is now evident a southward and a pronounced westward ecologic migration of this spider beyond the 100th meridian (beyond which, until 1963, this species had never been collected) as far west as the Pacific Coast.

The Brown Spider, *Loxosceles Reclusa*

The brown spider, *Loxosceles*, belongs to the family *Scytodidae*, the members of which are characterized by having six eyes and simple, external reproductive organs. The genus *Loxosceles* is further characterized by having a recurved row of anterior eyes, a low cephalothorax and a yellow-brown body. *L. reclusa* is a small spider, the female usually about 9 mm long and the male about 8 mm. The entire body is covered with hair and is usually dark brown in color. The cephalothorax is close to the ground, and to it are attached eight long legs. A further distinguishing feature is a purple-brown, violin-shaped stigmatum on the dorsum of the cephalothorax. (See Figure 2.)

The *Loxosceles* spiders usually spin a small, irregular web that is not used to capture its prey. They prefer infrequently disturbed places, and usually will be found in storage closets, around old clothing, and at other sites of the house or garage commonly used for storage. They hunt at night. Usually they attack man only in self-defense when disturbed. As might well be expected, most reported bites have occurred in bed at night or when the victim was donning clothes that had not been used for several months, or when he was removing materials from storage.[3]

Toxocology

The *Loxosceles* spider possesses two large glands connected to its fangs. One gland contains

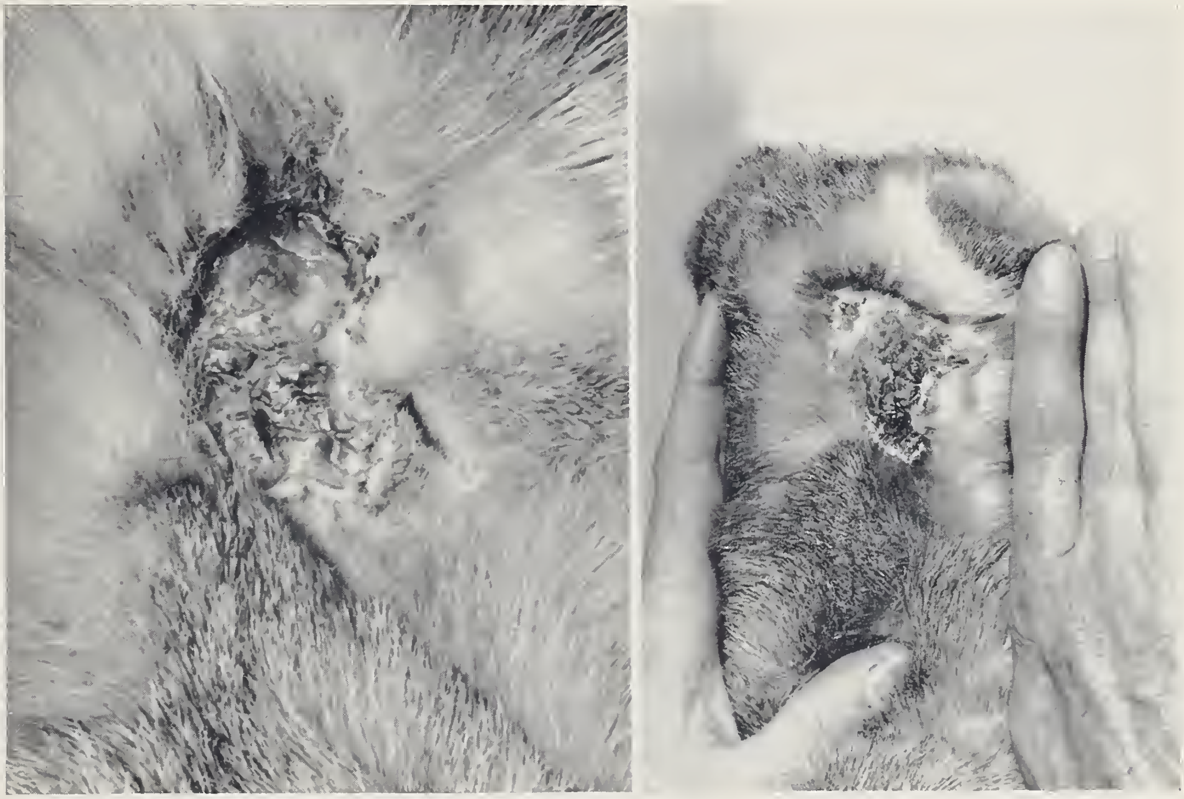


Figure 3.—Typical ulcer in experimental rabbit. Left frame shows lesion 12 days after bite by *Loxosceles* spider; right frame, after 15 days.

only a thick "gum" used to capture prey, the other gland contains the venom. Volume for volume, the venom of the *Loxosceles* spider is more virulent and pernicious than that of the rattlesnake, and is potentially more lethal than even that of the Black Widow spider. The components of the *Loxosceles* venom have not completely been isolated. The venom is known to contain at least three factors: (1) Levarteranol, (2) hemolysins which have not been completely separated, and (3) a "spreading factor" similar to that found in the venom of many snakes.

In laboratory experiments with rabbits, Wingo and Atkins noted that death may ensue within 12 hours after only two or three bites by *Loxosceles* spiders. On postmortem examination of these animals, ecchymosis and petechial hemorrhage was observed in the corporal muscles and gastric mucosa. Erosion of the gastric mucosa also was noted. Wingo and Atkins in addition demonstrated that animals that survived the initial attack by the *Loxosceles* spider had a resistance or immunity to subsequent attacks. Mackennon and Wilkind suggested the existence of a passive immunization to the venom of the *Loxosceles* spider and their observation was confirmed by Atkins and Wingo[2] in 1958.

Pathology

Many *Loxosceles* bites are benign (despite the venom toxicity) and, therefore, are of no medical concern; but a few are serious enough for the patient to consult a physician.

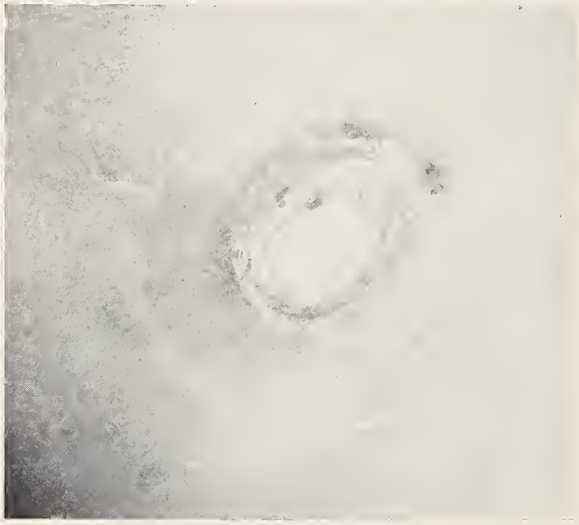


Figure 4.—Characteristic ulcer, about 4×5 cm, in a patient three weeks after bite by *Loxosceles reclusa* spider.

There are two clinical variants of necrotic arachnidism produced by the bite of the *Loxosceles* spider: The localized cutaneous necrotic arachnidism, the most commonly seen form, and severe systemic viscerocutaneous arachnidism.

The severity of the bite is directly proportional to the depth of penetration by the fangs and to the duration of the exposure. The bite of the *Loxosceles* spider produces a sting which is milder than that of the average bee, and for this reason may go completely unnoticed by the victim. Within several hours, a small bleb surrounded by an area of erythema appears at the site of toxic injection, later to be replaced by a white, edematous area. This edematous area will ultimately progress to a violaceous-to-black reaction which in turn will gradually be supplanted by the typical, brown-black eschar. The eschar usually sloughs within two to three weeks, leaving the deep, necrotic ulcer, characteristic of necrotic arachnidism (Figures 3 and 4).

The ulceration may extend down to the underlying muscle, but in the main does not involve the muscle itself. These ulcerated areas are characterized by extensive fat necrosis and are extremely slow to heal. Usually complete granulation and scar tissue formation takes from several weeks to months. Cultures of material taken from the area of ulceration will usually be negative for bacterial organisms during the early stages; however, secondary infection, usually with a species of *Staphylococcus,* may occur during the chronic stages.

Secondary ulceration may appear proximal to the primary lesion, perhaps due to the spreading factor in the venom.

Occasionally, the bite of the *Loxosceles* spider may result in a fulminating, systemic viscerocutaneous form of necrotic arachnidism. Such reactions usually consist of arthralgia, nausea, vomiting, restlessness, fever ranging up to 40°C (104°F), proteinuria, hemoglobinuria and a generalized scarlatiniform rash. Schenone,[10] in reporting 40 cases of necrotic arachnidism from Chile, Uruguay and Peru, described four in which the systemic viscerocutaneous form of the disease developed. Hemolytic anemia developed in two patients, but there were no deaths in the series. Minton[8] in 1964 reported a case of hemolytic anemia associated with necrotic arachnidism in a seven-year-old boy from Indiana.

Therapy

The treatment of necrotic arachnidism thus far has been primarily supportive and symptomatic. Since the venom of the *Loxosceles* spider is a viscerotoxin (cytotoxin), rather than a neurotoxin as is the venom of the Black Widow spider, calcium gluconate is not effective in treating the bites. Vasodilators have been used in an attempt to counteract the effects of the norepinephrine-like component of the venom. There have been reported instances of excellent results obtained from the use of local infiltrations of phentolamine (Regitin®) into the site of the bite. Steroids and antihistamines have both been tried. The results, however, are questionable.

In the severe, viscerocutaneous form of necrotic arachnidism treatment is again principally supportive and symptomatic. There has been a specific antivenom developed in South America which has been demonstrated to be very effective against the systemic effects of the venom of the *Loxosceles laeta* spider—the South American counterpart of *L. reclusa.*

When the eschar sloughs, leaving a large, ulcerative area with extensive fat necrosis, treatment consists of surgical debridement and skin-grafting. The debridement should be radical, including a wide area extending down to the fascia of the underlying muscle. Debridement and skin grafting may also be indicated if healing results in proliferative scar-formation.

Antibiotics are usually not indicated in the localized form of necrotic arachnidism, inasmuch as the areas of ulceration are usually sterile. If subsequent cultures from the ulceration should demonstrate the presence of a secondary infection, then appropriate therapy is certainly indicated.

Report of a Case

A 20-year-old white man was admitted to Queen of Angels Hospital in May 1964. After spending a night in a motel in San Diego, California, he discovered a blister on the sole of his right foot and a reddened area over the left buttocks. (The patient had not recently been in any area known to be a habitat of the *Loxosceles* spider.) The following day, the bleb on the sole of the right foot opened, and a clear, whitish fluid was expressed. During the next several days this area enlarged progressively and ulceration began. By the end of the third week, an irregular cutaneous ulcer, 5×12 cm, with extensive fat necrosis, occupied a large part of the lateral aspect of the right foot (Figure 5). During this same period the patient had increasing pain over the foot and buttocks. Within the next two weeks the area over the left buttocks showed progressive erythema, becoming violaceous. By the end of the second week a dark brown-black eschar had formed over this area. The eschar then sloughed, leaving a deep ulcerated area of extensive fat necrosis (Figure 6). The patient refused surgical therapy and returned home.

Figures 5 and 6 were submitted to Dr. C. W. Wingo at the University of Missouri. Dr. Wingo said: "The ulcers in your photographs are typical of those we see in Missouri and adjoining states

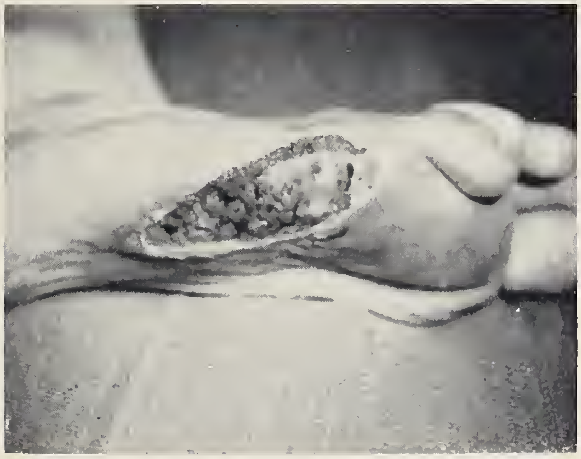


Figure 5.—Extensive ulceration with fat necrosis over the lateral aspect of the right foot three weeks after what appears to have been a spider bite.

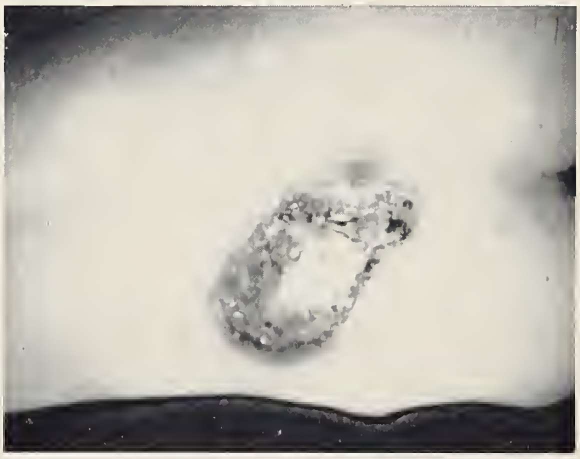


Figure 6.—Extensive ulceration with fat necrosis over the left lumbosacral area three weeks after what is assumed to have been a spider bite.

following bites of *Loxosceles reclusa.* I know of no insect or other arthropod in the United States capable of causing necrotic ulcers. I doubt very much that it was caused by any agent other than a spider, and I feel strongly that it was a species of *Loxosceles.*"

Summary

Bites by Missouri Brown spider, *Loxosceles reclusa,* which has not yet been reported found in the Western United States, can cause extensive necrotic ulcerations at the site of injection.

Necrosis of the kind reported from such bites was observed on the foot and buttocks in a patient who several days earlier had wakened in a San Diego motel to find what appeared to be stings of some sort at the sites where the more severe lesions later developed. Pictures of the necrotic ulcers were sent to a Missouri physician who was conversant with necrotic arachnidism, and he said that they were "typical of those we see . . . following bites of *Loxosceles reclusa.*"

GENERIC AND TRADE NAME OF DRUG

Phentolamine—*Regitin.*

REFERENCES

1. Atkins, J. A., Wingo, C. W., and Soderman, W. A.: Probable cause of necrotic spider bite in the midwest, Science, 126:73, 1957.

2. Atkins, J. A., Wingo, C. W., Soderman, W. A., and Flynn, J. E.: Necrotic arachnidism, Am. J. Trop. Med., 7:165-184, 1958.

3. Comstock, Spider Book, 595.4c73—Doran & Co., New York, 315-316, 1948.

4. Gertsch, W. J., and Mulaik, S.: Spiders of Texas, Bull. Am. Mus. Nat. Hist., 77:307-340, 1940.

5. Lessenden, A. M., and Zimmer, L. K.: Brown spider bites, J. Kans. Med. Soc., 61:379, 1960.

6. Nance, W. E.: Hemolytic anemia of necrotic arachnidism, Am. J. of Med., 31:801-806, 1961.

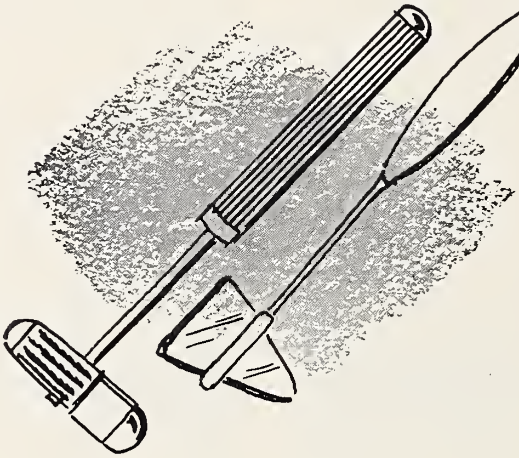
7. Pfizer, Charles & Company: Brown spider, Spectrum, 8:214-216, 1960.

8. Olson, C., and Minton, S. A.: Spider bites and hemolysis, Pediatrics, 33:283-284, 1964.

9. Pitts, N.: Necrotic arachnidism, New Engl. J. Med., 267:400-401, 1962.

10. Schenone, H.: Arachnidism by Loxosceles laeta, Arch. of Derm., 83:139-142, 1961.

11. Wingo, C. W.: Personal communications.



Cysticercosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

Dr. Larry Cardoza*: The patient is a 31-year-old married woman who came to the United States from Mexico five years ago. For the past four years she has had intermittent headaches. In the six months preceding admittance to hospital, headache had become persistent and was occasionally associated with vertigo and sharp shooting pains in both ears. In addition, during the two to three weeks before the first admission to hospital four months ago she had vomited two to three times daily.

Results of physical examination at the time of the first admission were unremarkable except for the examination of the nervous system. The cranium was of normal configuration and the pupils were equal and reactive. Bilateral papilledema with retinal edema, a flame-shaped hemorrhage of the right retina and an increased blind spot in the left eye were present. No abnormalities were noted on examination of the motor, sensory, and cerebellar systems and the reflexes were equal and active.

The following pertinent laboratory data were obtained: Leukocytes numbered 9,000 per cu mm of blood with 7 per cent eosinophils. Results of examination of the stools for ova and parasites were negative. A brain scan, electrocardiogram, electroencephalogram, cervical spine films and orbital films were within normal limits. Vertebral and bilateral carotid arteriograms suggested tonsillar herniation and ventricular dilatation. A pneumoencephalogram was attempted without success, so a ventriculogram was done via burr hole. This was interpreted as demonstrating a space-occupying lesion of the left lateral ventricle and ventricular dilatation. Consequently, left frontal temporal craniotomy was performed.

When no evidence of tumor was found on transcortical exploration of the left lateral ventricle, radio-opaque material was instilled into the anterior portion of the third ventricle and x-ray films were taken. Stenosis of the distal aqueduct was noted and the films were interpreted as being compatible with inflammatory changes, possibly secondary to parasitic or fungal disease. In the postoperative period, the severity of headaches decreased and the intracranial pressure was normal.

The patient left the hospital three weeks after operation with a diagnosis of partial aqueductal stenosis secondary to inflammatory disease of unknown cause.

For the next month the patient was observed intermittently in Neurology Clinic and she continued to complain of mild headaches. Five weeks after the initial stay in hospital she was readmitted to the Neurology Service because of persistent headache and, in addition, fuzzy vision of the left eye. Bilateral papilledema with retinal edema and fresh hemorrhages were observed. A ventricular tap was done via burr holes, and the opening pressure was 280 mm of water. The fluid was described as cloudy with 5 leukocytes and 5,000 erythrocytes per cu mm. Subsequently, florid staphylococcal meningitis developed and was successfully treated with a three-week course of antibiotics.

During this period there was persistent eosinophilia of 18 to 23 per cent. There were no palpable subcutaneous nodules, and skull and chest films did not show intracranial or pulmonary calcifications. Latex fixation tests for trichinosis were negative, and serological tests for coccidioides were non-reactive. Intermediate strength purified protein derivative (PPD) and coccidioidin skin tests were positive. A Casoni skin test which utilizes the echinococcus antigen was negative in both immediate and delayed reaction; however, a blood specimen which was submitted to the Communicable Disease Center in Atlanta for a hemagglutinin test against cysticercus was reported to be positive.[†] Three additional stools were negative for ova and parasites. Cultures of the cerebrospinal fluid for fungus were negative as was an India ink preparation for Cryptococcus. The final diagnosis was: Partial aqueductal stenosis secondary to central nervous system cysticercosis. A cerebrospinal fluid shunting procedure was recommended for this patient, to be done as soon as it could be established that she no longer had an active infection of the nervous system.

---

*Fourth-year student in Medicine.

Dr. Warren M. Russell[*1]: In x-ray films the sella turcica was observed to be enlarged and the posterior clinoids partially eroded, indicating increased pressure (Figure 1). A pneumoencephalogram revealed dilatation of the lateral ventricles and third ventricle (Figure 2). Pantopaque was introduced into the third ventricle outlining a dilated aqueduct of Sylvius which narrowed distally to nearly complete obstruction (Figure 3). Additional views showed a distortion of the fourth ven-

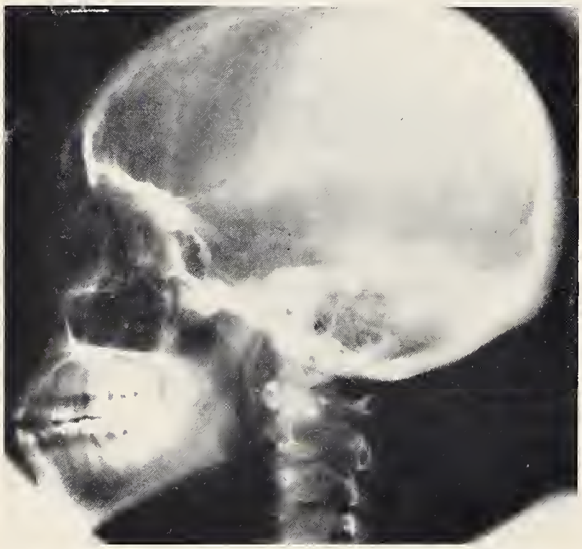


Figure 1.—View of enlarged sella turcica with posterior clinoids partially eroded.

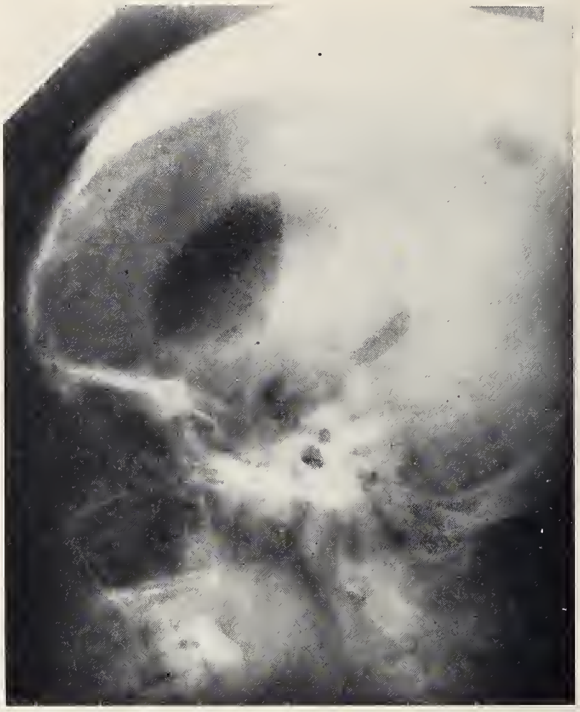


Figure 2.—Pneumoencephalogram showing dilatation of lateral ventricles and third ventricle.

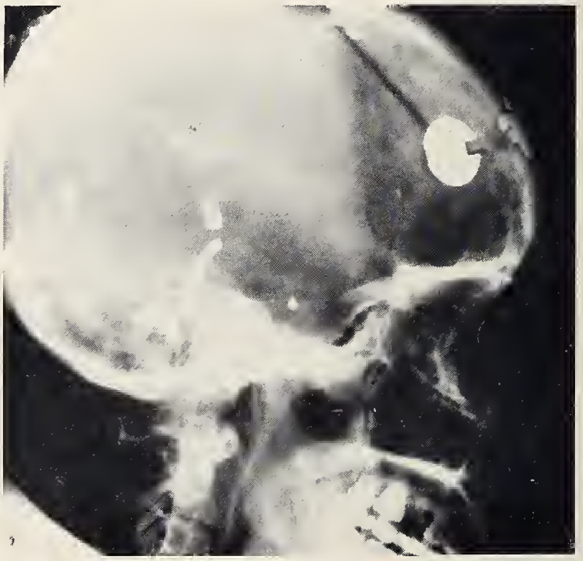


Figure 3.—Outline of dilated aqueduct of Sylvius which narrowed distally to almost complete obstruction.

[†] The following information about the test was supplied by Irving G. Kagan, Ph.D., Chief, Parasitology Unit, Mycology and Parasitology Section, Public Health Service Communicable Disease Center, Atlanta:

Two antigens are used in the test. One is prepared from whole adult worms of *Taenia saginata* and the other from cysticerci in pig muscle of *T. solium*. In evaluation studies, the whole worm antigen is more specific than the cysticercus antigen. However, both antigens cross-react with sera from patients with echinococcosis (52 per cent) and schistosomiasis (39 per cent).

Results obtained in Mexico in a comparison of three tests—precipitin indirect hemagglutination and complement fixation—showed that the indirect hemagglutination test was the most sensitive procedure. Because of the limited number of cases in the United States, the tests for cysticercosis have not been thoroughly evaluated. High titers have been obtained in tests by the Communicable Disease Center with a limited number of sera from proven cases. Since the tests are quite sensitive, a negative reaction may have some significance.

[*1] Assistant Professor of Radiology.

tricle. The appearance was consistent with an inflammatory process involving both the aqueduct and the fourth ventricle. Bilateral carotid and vertebral arteriograms only confirmed the presence of hydrocephalus. The chest film was within normal limits.

Dr. Lloyd H. Smith, Jr.*[2]: This is a very interesting patient and a most difficult therapeutic problem. I think it is fair to say that at the time of operation everyone confidently expected that a brain tumor would be demonstrated by craniotomy. This did not prove to be the case. I would like to point out that the attending physician on the medical ward at the time the patient returned with purulent meningitis was Dr. Walter Strauss, and that he made the suggestion that cysticercosis might be the etiological factor in the production of increased intracranial pressure and aqueductal obstruction. I think that this diagnosis has been only equivocally established, but it appears to be the most likely explanation of this woman's illness. We have asked Dr. Strauss to review the evidence for this diagnosis and to discuss the problem of cysticercosis.

Dr. Walter G. Strauss*[3]: This patient was discharged from hospital with the diagnosis of cysticercosis. I could not resist going to the record room to find out how often the diagnosis of cysticercosis had been made at this hospital. It had been made three times previously. I would like to present the three cases to you because an important point can be made about each.

Reports of Three Previous Cases

At this hospital it was first made in 1955 when a 35-year-old housewife noted a tender lump over the right scapula. Her main symptom was extreme anxiety, for her brother had died of a sarcoma at age 22 and she was afraid that she might also have this disease. X-ray films of the chest and skull showed no abnormalities. An operation was done and the mass was excised. It was a single cysticercus. The patient was reassured and well until 1959 when she had tinnitus and headache. No particular abnormalities were found throughout the workup until an electroencephalogram showed a left-sided focus. A ventriculogram demonstrated a left cerebellar cyst, which was subsequently removed. The patient died postoperatively. Sections of the operative specimen showed that it was a hemangioblastoma and not a cysticercus.

The second case was that of a 28-year-old man who had a craniotomy at a hospital in San Jose, California. His symptoms at that time were dizziness, headaches and convulsions. At operation a cyst was removed which was clearly a cyst of cysticercus. He was admitted here for two days for reasons which are unclear. At that time he was in the stage of convalescence and was observed and discharged.

The third case was that of a 31-year-old woman who had had seizures for three years. Electroencephalograms showed a left cerebral focus. A pneumoencephalogram was normal; however, x-ray studies of various regions of her body showed at least one soft-tissue calcification, 1×5 mm, in the abdomen. No serological studies were done at the time but the presumptive diagnosis was cysticercosis.

I found a remarkably similar geographic background in these three patients and in the patient presented today. All were of Mexican origin. If we derive one moral from this story it is this: When Mexican patients are examined because of epilepsy or some obscure intracranial disease, the physician should think of cysticercosis. The observation of cysticercosis in persons of Mexican origin may reflect only our own experience here in San Francisco. However, the disease is certainly not limited to Mexico. It is prevalent in India and other parts of Asia and Africa, but rare in Great Britain and in the United States. I have never seen a case of infestation with the pork tapeworm adult and the diagnosis of pork tapeworm has never been made at this hospital, or to my knowledge in San Francisco.

What Is Cysticercosis?

Cysticercosis is the infection of tissues with the intermediate larva of the pork tapeworm, *Taenia solium*. The life cycle is shown in Figure 4. The life cycle begins with the human, passes through the pig, and then passes back into the human. I have no picture of an adult tapeworm but one can visualize the man shown in Figure 4 as having in his abdomen a tapeworm of some four to perhaps 15 feet in length. Through the stools, this worm sheds mature segments which contain the ova. In general the segments are shed whole and fall onto the ground. In order for the life cycle to continue, these mature proglottids must fall onto the ground where the usual intermediate host, the pig, picks them up during foraging and swallows them. In the abdomen of the pig, the proglottid dissolves; in fact, the outside of the egg dissolves and out comes a little six-hooked embryo which is approximately 30 micra in diameter. This embryo scratches its way into the intestinal wall, finds its way into the portal circulation, and is carried throughout the body of the pig. It comes to lodge in the muscles of the pig and encysts. This cyst is the cysticercus. Pork which is thus infected is often infected heavily, and is called measly pork. If eaten by man in insufficiently cooked pork, a cysticercus can become an adult worm in the intestinal tract.

---

*[2] Professor and Chairman, Department of Medicine.

*[3] Assistant Clinical Professor of Medicine.

Epidemiology

The mature tapeworm in man does not cause any great disturbance, no more than perhaps a beef tapeworm which is the common one we see in California. Unfortunately, the eggs are infective not only to the pig but to man himself so that man can be not only the definitive host of the mature tapeworm but also the intermediate host harboring the cysticercus.

Approximately 25 per cent of persons with cysticercosis actually have an adult tapeworm. They become infected from eggs of their own tapeworm, either through the anus-to-mouth route or perhaps even by retrograde peristalsis. From these observations it follows that all patients with pork tapeworm must be carefully isolated. Stool isolation must be practiced for fear of disseminating the eggs to the patient or to other persons. The other 75 per cent of persons with cysticercosis—and this includes our patient today—simply pick up the eggs from somebody else who has the tapeworm. This accounts for the rarity of cysticercosis in the United States. In this latter mode of acquisition, infestation is often not very heavy. Only a very few eggs are picked up and carried to various organs.

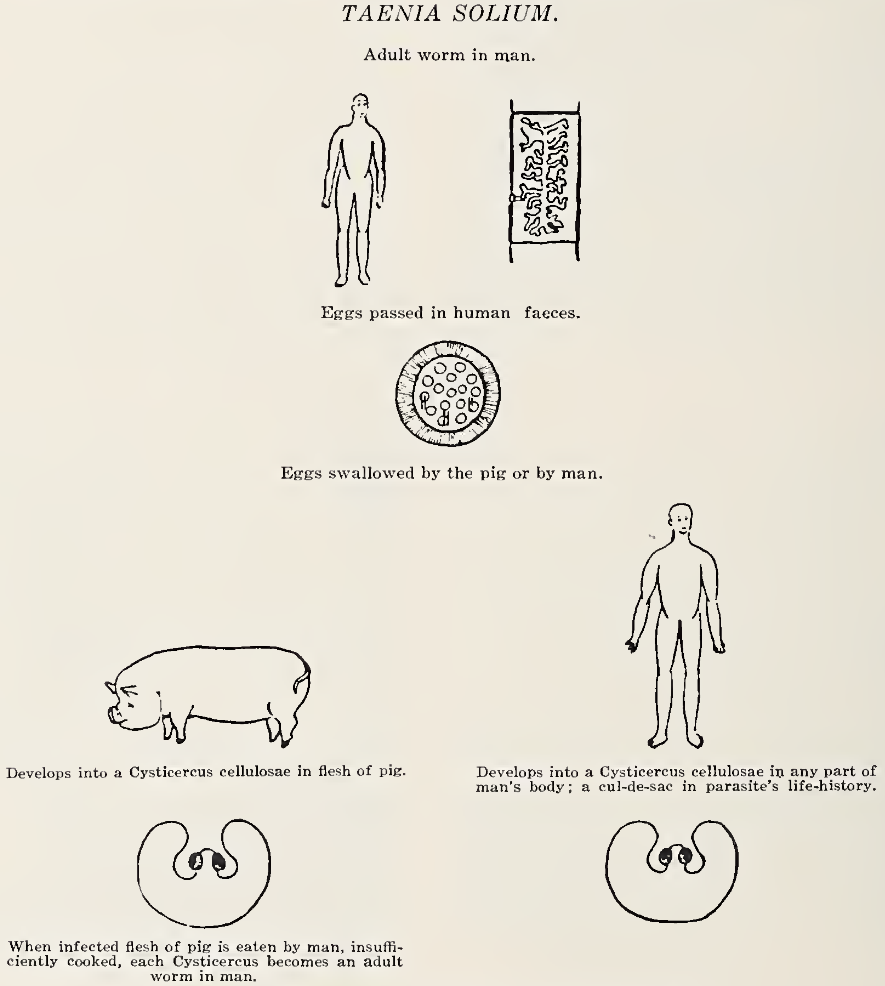

TAENIA SOLIUM.
Adult worm in man.
Eggs passed in human faeces.
Eggs swallowed by the pig or by man.
Develops into a Cysticercus cellulosae in flesh of pig.
Develops into a Cysticercus cellulosae in any part of man's body; a cul-de-sac in parasite's life-history.
When infected flesh of pig is eaten by man, insufficiently cooked, each Cysticercus becomes an adult worm in man.

Figure 4.—Life cycle of cysticercus, *Taenia Solium.*

Pathologic Changes

In human beings, the little embryo as it is carried by the bloodstream seems to have a predilection for certain tissues—brain, eye, heart and also muscle and subcutaneous areas. For some reason, the choroid plexus seems to catch these embryos as they circulate and then seems to extrude them into the cerebral fluid. As this occurs, growth of the embryo also occurs. The little embryo hollows out and a little blister or cyst forms, although it may also float free for awhile in the cerebral fluid in the ventricles.

The pathological section of a mature cysticercus in the eye is shown in Figure 5. The rather dark organism in the center is the cysticercus, and the little dots are cut sections through the scolex, the immature end which is waiting to become the head of a tapeworm. As the little cysticercus matures, it grows from 30 micra to its more mature measurements of 2 to 7 millimeters. One can visualize that, as the cysticercus floats free, it might become stuck at the aqueduct of Sylvius or perhaps at the foramina of the fourth ventricle, the foramina of Magendie and Luschka, leading to the development of hydrocephalus. The cysticercus also lodges in the brain tissue itself, and for the most part causes relatively little reaction until it dies. This may occur after three years of infection. It has been said that the cysticercus can live as long as 15 years. When it dies, tissue reaction occurs; swelling, eosinophilia and edema are very prominent at this time. This is when symptoms may appear. Eventually, calcification occurs and the cysticercus may become visible radiographically. Figure 6 shows an x-ray film of the abdomen of a patient with calcified cysticerci.

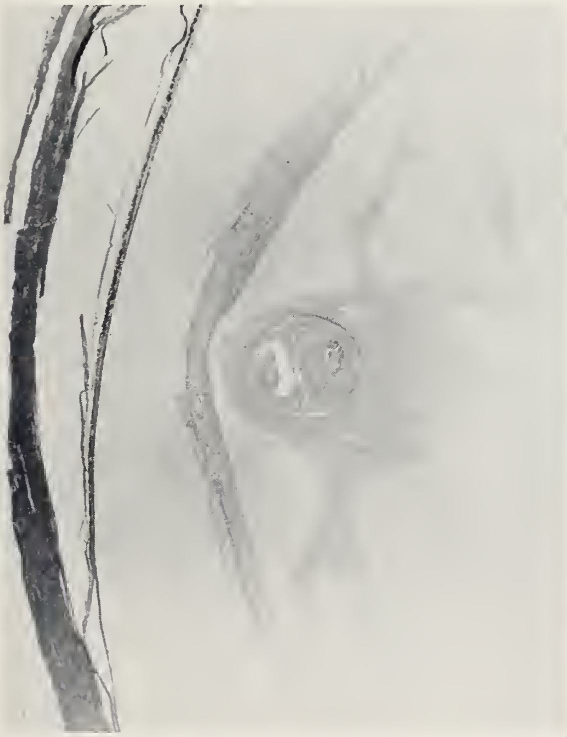


Figure 5.—Pathological section of mature cysticercus in eye. Dark organism at center is cysticercus and the little dots are sections through the scolex, which becomes the head of a tapeworm (× about 10).

Symptoms and Diagnosis

As far as symptoms are concerned, these depend primarily on where the cysticercus lodges. Hydrocephalus and seizures are the most common symptoms of cerebral cysticercosis. Cysticercosis of muscles may not cause symptoms. If the cysticercus lodges in the heart, various degrees of heart failure or cardiac arrhythmias may occur. On physical examination, relatively little can be seen unless the examination reflects the intercerebral disease. Sometimes, subcutaneous nodules can be felt, and it is certainly helpful in establishing the diagnosis if more than one can be felt. Peripheral eosinophilia, and calcifications on x-ray examination may give one a hint as to the diagnosis.

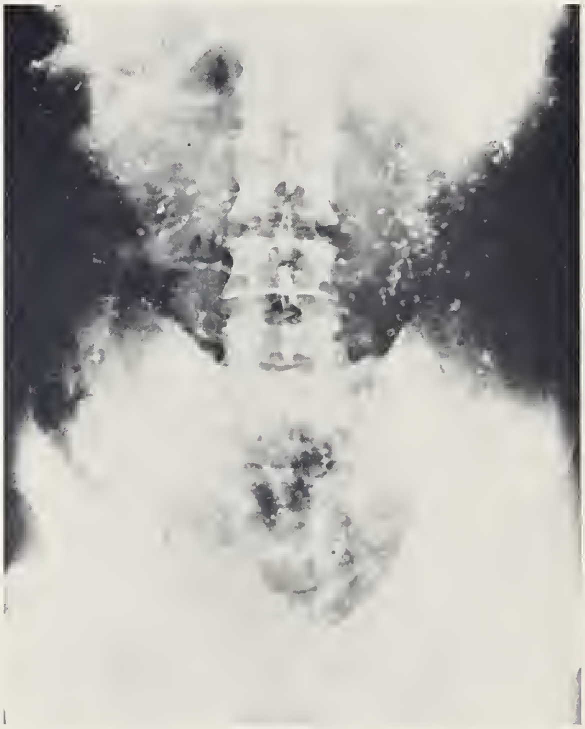


Figure 6.—X-ray film of abdomen of a patient with calcified cysticerci.

The cerebral spinal fluid is said to have a low sugar content if the cysticercus is still alive. Various kinds of cells may appear in the spinal fluid including eosinophils. The Casoni skin test employs the fluid from yet another cysticercus-like animal, the hydatid cyst. This test is readily available. Fluid withdrawn from a sheep that is found to have the cyst is filtered and the antigen thereby obtained. But it is not a very specific antigen insofar as only about 50 per cent of patients with cysticercosis react to it. So far as I know, the only place in the United States that performs serological tests on the blood and spinal fluid is the Communicable Disease Center in Atlanta.

Treatment

What about treatment? We do have certain anthelmintics which conceivably could kill the cysticerci. I do not know if all of these have been tried in experimental animals but I would ask the question: Is this desirable? If the cysticerci die one by one over a period of time they produce relatively little local inflammation. This seems to me to be preferable to having them all die at once, producing either an overwhelming anaphylactoid reaction or an increase in the spinal fluid pressure. In any case, we do not use anthelmintic treatment. Neurosurgical treatment is, of course, employed when the symptoms become as severe as in the patient presented today. In a patient with seizures, antiepileptic measures are used.

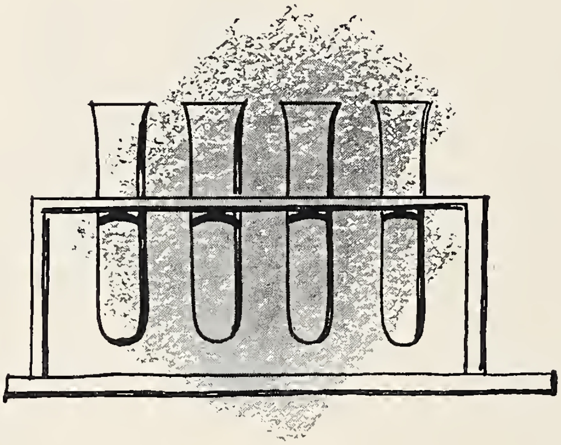
Prognosis is variable. There are many people walking around who have a few asymptomatic cysts; they probably never get into any trouble. In the patient presented this morning, the prognosis is quite a bit more doubtful and deaths from cerebral cysticercosis are not unknown. On the other hand, if the cyst can calcify and if patients can overcome this acute illness, it is conceivable that they will recover and be quite well.

Editor's Note: Three months after the patient was presented at the Medical Staff Conference, she underwent a neurosurgical shunting procedure from which she recovered without difficulty. At present, six months later, the patient continues to have headache and some difficulty in walking.

Recent Summaries in the Literature

1. Dixon, H. B. F., and Hargreaves, W. H.: Cysticercosis, Quart. J. Med., 13:107, 1944.

2. Arseni, C., and Samitca, D. C.: Cysticercosis of the brain, Brit. Med. J., 31 August 1957, pp. 494-497.



Editor
DWIGHT L. WILBUR, M.D.
•
Assistant to the Editor
ROBERT F. EDWARDS
For information on preparation of manuscript, see advertising page 2

Policy Committee—Editorial Board
JAMES C. MacLAGGAN, M.D., San Diego
JOHN G. MORRISON, M.D., San Leandro
WILLIAM F. QUINN, M.D., Los Angeles
JOSEPH W. TELFORD, M.D., San Diego
CARL E. ANDERSON, M.D., Santa Rosa
HELEN B. WEYRAUCH, M.D.
San Francisco
DWIGHT L. WILBUR, M.D., San Francisco

California Medicine

EDITORIAL

Health Manpower and Medical Associations

MAJOR QUESTIONS to be considered by the National Advisory Commission on Health Manpower which was established by President Johnson in May of this year have been conveyed by Peter S. Bing, M.D., Executive Director of the Commission, to a wide variety of interested persons and organizations:

1. What factors will be most important to intelligently forecast public and private demands for health manpower in the coming decade?
2. What alternatives are feasible to increase the productivity of existing health personnel?
3. What should be the role of the medical consumer in determining the organization of medical services and in assessing their quality?
4. Where does the responsibility lie for meeting the demands for medical manpower during the next decade?

All of the questions involve matters in which the American Medical Association and component state medical associations, serving as representatives of the medical profession and as "physicians to the community," have keen interest.

Some of the questions bring problems into focus and give rise to conjecture about how they will be solved. A "drastic shortage of health manpower" has been recognized by the AMA Board of Trustees which has established a Committee on Health Manpower to find ways to deal with the problem.

Efforts to "increase the productivity" of health personnel can be expected, for example, to seek ways of using triage to the better advantage of both physician and patient, and indeed of everyone involved in the care of patients. The use of computers in many clerical ways and possibly in dealing with some medical problems is an exciting new possibility. It can be conjectured further that some increases in efficiency will come from realignments in the structure of medical practice, brought about deliberately or by evolution.

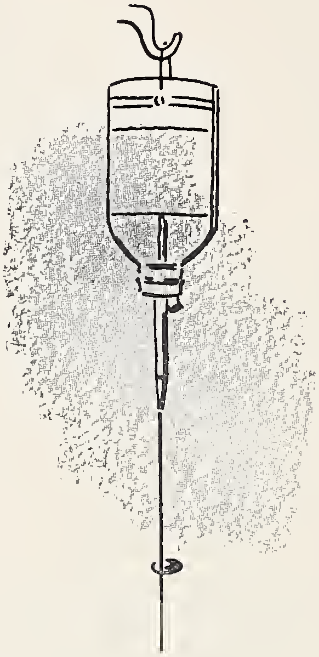
Obviously there will be pressures for the organization of new medical schools, for the expansion and improvement of existing schools and for recruitment of more students of high quality, not only as candidates for the M.D. degree but also for training in the allied health professions and services. Searches for new methods of teaching also can be expected.

These are all matters of vital concern to individual practitioners and to the organizations that represent collectively the best attitudes of physicianship, for at all points the conditions of practice and the quality of medical care are involved. Some of the solutions will be concerned in the main with the economics of medicine—with money and the availability and distributions of medical care. Some will reach deep into the great spiritual traditions of medicine. In all of them the energy, the knowledge, the developed ability and the cooperation of medical organizations can be profoundly useful.

Whatever may be the changes that are found necessary to expand medical care and to improve the efficiency of providing it, we as physicians must make sure that our own interests and those of our patients are fully weighed and strongly advocated. The AMA and our California Medical Association are well grounded in just the kind of work that may be anticipated from the studies of the National Advisory Commission on Health Manpower.

Through our experienced committees of physicians and our able employees we are in a position to exercise the strong leadership that must be expected of our association in serving as "physicians to the community." As a case in point, the AMA has a strong and active Committee on Health Manpower which is looking into questions much like those posed by the National Commission. And in California the CMA is well represented in a newly formed statewide joint council of voluntary health agencies which will be concerned with recruitment and the development and efficient use of health manpower. More, we have excellent liaison with many of the allied health professions, with medical schools and with the administrative and legislative functions of government that are likely to be involved.

It is more through foresight than fortuity that we now stand ready to carry out one of the purposes for which our organization exists.



California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 525th Meeting of the Council, San Francisco, Hilton Inn, 29 October 1966.

The meeting was called to order by Chairman Anderson, at the Hilton Inn near San Francisco on Saturday, 29 October 1966, at 9:05 a.m.

A quorum present and acting (full roll call, including names of invited guests, appears in item 43).

1. *Minutes for Approval*

Minutes of the 524th meeting of the Council, held 17 to 18 September 1966 were approved pending clarification of the definition of "medical and surgical technicians" in Item 24. The Commission on Allied Health Professions and Services will report on this subject at a future meeting.

2. *Studies of Deaths in California*

Doctor Malcolm Watts brought to the attention of the Council that official action had not been taken on a proposal which received favorable consideration at the 17 to 18 September meeting—to initiate ongoing studies of deaths in California. The proposal was described as an effort to study and improve the quality of patient care.

ACTION: Voted to refer the proposal to the Scientific Board for study and report back to the Council.

3. *Care of Patient Workshops*

Another subject discussed at the 17 to 18 September Council meeting, "Care of Patient Workshops," was raised by Doctor Watts, who stated that the workshops would be designed to stimulate more "personalization" in all types of health care.

ACTION: Voted to request the Scientific Board to look into the feasibility of conducting "Care of Patient Workshops" and to report back to the Council.

4. *Reports to the Public*

Doctor Watts' final suggestion resulting from the last Council meeting was that the Council take action on the idea of releasing reports to the public based on the information presented and positions taken at meetings of the CMA Council. No formal action was taken because Communications is already releasing such statements, but it was recommended that the Commission on Communications be notified of the request.

JAMES C. MacLAGGAN, M.D.	President
JOHN G. MORRISON, M.D.	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH W. TELFORD, M.D.	Vice-Speaker
CARL E. ANDERSON, M.D.	Chairman of the Council
ALBERT G. MILLER, M.D.	Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D.	Secretary
DWIGHT L. WILBUR, M.D.	Editor
EDGAR WAYBURN, M.D.	Acting Editor
HOWARD HASSARD	Executive Director

General Office, 693 Sutter Street, San Francisco 94102 • 776-9400

ED CLANCY . . . . Southern California Office

1515 N. Vermont Avenue, Los Angeles 90027 • 663-8071

5. *1970 Congress on Occupational Health*

The Council received a letter from Doctor Packard Thurber suggesting that CMA extend a written invitation to the AMA Council on Occupational Health to hold its 1970 Congress in Los Angeles.

ACTION: Voted to invite the AMA Council on Occupational Health to hold the 1970 AMA Congress on Occupational Health in Los Angeles.

6. *Report of the President*

President MacLaggan reported that the Crippled Children's Advisory Committee is attempting to redefine some diseases to include a wider range of treatable conditions under the program, as well as studying the physician eligibility for the program.

Doctor MacLaggan also reported on the Woman's Auxiliary Fall Conference and requested that an appropriation of $400.00 be made for the Woman's Auxiliary hospitality room during the next Annual Session.

ACTION: Voted to approve the appropriation of $400.00 to the Woman's Auxiliary.

7. *Report of the President-Elect*

President-Elect Morrison reported that as he has visited the various county societies he has observed that most of the non-executive societies are receiving very little direction or assistance from CMA or other societies, and he feels a need for guidance exists. Doctor Morrison asked that the Medical Executives Conference establish a study committee to look into ways to assist the non-executive societies.

ACTION: Voted to refer the matter to the Medical Executives Conference for study and report back to the Council.

8. *New Committee Members*

The following nominations, most of them to fill vacancies or supplement membership on various CMA Committees and Commissions, were offered:

Advisory Committee to CMA Representatives on the California Coordinating Committee on Regional Medical Programs—Malcolm S. M. Watts (Chairman), San Francisco; Leland B. Blanchard, San Jose; Harold Griffeath, San Francisco; Donald Petit, Los Angeles; Saul Robinson, San Francisco; David Rubin, Los Angeles; Justin J. Stein, Los Angeles; David A. Wood, San Francisco.

Subcommittee on Industrial Medical Fees—H. Dean Hoskins, Oakland; Roger Isenhour, San Diego; Homer Pheasant, Los Angeles.

Ad Hoc Committee on Medical Libraries—Harold Kay (Chairman), Oakland; William P. Longmire, Los Angeles; Donald Petit, Los Angeles; Abe Sirbu, San Francisco.

California Interagency Council on Cigarette Smoking and Health—James Keran (CMA Representative), Berkeley.

Committee on Scientific Assemblies — Mr. Claron Oakley (Consultant), Los Angeles.

Committee on Organizational Review and Planning (additional members)—Harold Chope, San Mateo; Howard House, Los Angeles; Charles Miller, Redding; John Rumsey, San Diego; John Tupper, Dean, Davis.

ACTION: Voted approval of the above nominations.

Councilor Kaiser asked that his negative vote be recorded regarding nominees to the Committee on Organizational Review and Planning.

9. *California Coordinating Committee on Regional Medical Programs (P.L. 89-239)*

Doctor MacLaggan reported that the application for a grant submitted by the California Coordinating Committee had received favorable action and that the money would be forthcoming. He also recommended that California Medical Education and Research Foundation (CMERF) be designated as the fiscal agent to act for the California Coordinating Committee.

ACTION: Voted to approve the designation of CMERF as the acting fiscal agent for the California Coordinating Committee on Regional Medical Programs.

Doctor Teall remarked on the reasoning behind the appointment of an advisory committee (composed of Scientific Board members) to the CMA representatives on the California Coordinating Committee. He pointed out that it was only logical that such a committee be appointed to advise the CMA representatives on projects which concern postgraduate education.

10. *Discharge of P.L. 89-239 Task Force*

Doctor James MacLaggan recommended to the Council that the Task Force on Public Law 89-239 be discharged since its duties had been assumed by the California Coordinating Committee on Regional Medical Programs and CMERF.

ACTION: Voted to discharge the Task Force on Public Law 89-239 with thanks.

11. *H.R. 18225 (Title 19 Amendments in Congress)*

Mr. Howard Hassard reported that H.R. 18225 died with the adjournment of Congress, though it is probable that amendments to Title 19 will be reintroduced at the next Congressional session.

Mr. Paul Ward, administrator of the State Health and Welfare Agency, reported in some detail on the proposed amendments to Title 19, and gave a preview of what might be expected to come out of the next session of Congress with regard to Title 19 limitations and changes. He reported that due to the New York plan, which had received so much publicity, there was sure to be a limitation on the amount of money to be spent under the Title 19 program, and described proposals for limiting funds that received the most acceptance by the Interim Committee. He mentioned other amendments which were likely to be included in the bill: Buying in under Title 18-B for medically needy over 65, redefining comparability of benefits due to alterations in other portions of the law, and providing matching funds for administrative purposes to agencies other than the administering state agency. Mr. Ward said that he hoped to be able to guide other states into molding Title 19 into what was originally intended with the elimination of categories and eligibity for the program based entirely on need of the individual.

12. *AMA Delegation*

Doctor Burt Davis reported that the CMA Delegation to the AMA had had a successful meeting with the Council on Friday night, 28 October. He said that the Delegation found this meeting most beneficial in solidifying ideas on major issues that were likely to come before the AMA House of Delegates at its upcoming meeting. Doctor Davis announced that the next caucus of the Delegation would be 4:30 p.m. on Sunday, 27 November, in Las Vegas.

13. *Finance Committee*

Chairman Kay reminded the Council that the annual audit of the California Medical Association and its related organizations had been mailed to Councilors for their review.

Doctor Kay also informed the Council that the Trustees of CMA had purchased 45 more frontage feet on Sutter Street contiguous to the headquarters office, increasing the total frontage to 90 feet, and therefore the value of the organization's holdings.

14. *Conference of Component Society Officers*

Doctor Dale Ritter, chairman of the Program Committee for the 1967 Conference of Component Society Officers, reported that planning is progressing for the 14 January meeting, to be held at the Airport Marina Hotel in Los Angeles. He said it was hoped that Jesse Unruh, Speaker of the State Assembly, and John P. Carmichael, of the *Chicago Tribune,* would be among featured speakers at the meeting.

15. *Role of Medicine in Society*

Chairman Watts presented to the Council a report, "Prologue and Perspective," produced by the Committee on the Role of Medicine in Society. It is the first in a series of four such reports; the remaining three will deal with "Quality in Health Care," "The 'Creative Partnership' for Health" and "Organizing for Better Health Care."

The Committee requested that the Council receive the Report and authorize its distribution to component medical societies and physician members of the CMA upon request. Discussion followed on the Report and Appendix A.

ACTION: Voted to receive the Report and authorize its distribution to component medical societies and physician members of the CMA upon request, with the deletion of Appendix A.

16. *Recommendations on County and Teaching Hospitals*

On behalf of the Task Force on P.L. 89-97, Chairman Teall offered to the Council for its approval a statement on the reimbursement for professional services in county and teaching hospitals, as the Council had charged the Task Force to do. The proposed statement was discussed and amended to read as follows:

1. In the interests of achieving the objective of mainstream medical care, the California Medical Association reaffirms its policy:
   (a) that medical staff organizations should be in conformity with (1) the rules of the Joint Commission on Accreditation of Hospitals; and (2) the Model Medical Staff Bylaws of the CMA, and

(b) that hospitals should not benefit financially from payment for physicians' services nor should physicians benefit from payments for hospital services.

2. The practice of medicine offers many opportunities for experimentation in the provision, organization, and financing of medical care. Both individual and group practice arrangements have important roles to play in providing good medical care in the best public interest. Each should be encouraged to develop new and creative approaches in providing patient care in county and teaching hospitals.
3. (a) When professional care is provided to a paying or paid-for patient in a county or teaching hospital by a physician on an individual private practice arrangement, reimbursement of the physician should be based on the criteria of usual, customary, and reasonable charges. However, when such professional care is provided by the physician as a member of a group or association, reimbursement should be based on the reimbursement formula appropriate to any similar private group practice arrangement.

   (b) No reimbursement should be sought from public or privately financed insurance for physician's services in teaching hospitals, or other county hospitals or other medical facilities which do not provide comprehensive or specialized services comparable to those elsewhere in the community.

ACTION: Voted to approve the statement on Reimbursement for Professional Services in County and Teaching Hospitals, as amended.

17. *Discharge of P.L. 89-97 Task Force*

Chairman Teall recommended that his Task Force on P.L. 89-97 be discharged of its duties in that the group had been organized on an ad hoc basis and that standing committees and commissions could now take over the problems that might arise.

ACTION: Voted to discharge the Task Force on P.L. 89-97 with thanks to Doctor Teall and other members for their tremendous efforts.

18. *State Legislation*

Doctor Kilroy, chairman of the Committee on Legislation, reported to the Council that there will be hearings on A.B. 5 early in December. He also informed the Council of a hearing concerning drug prices, to be held on 22 November 1966 in Sacramento beginning at 10:00 a.m. Discussion followed on whether or not CMA should present testimony at this hearing.

ACTION: Voted to ask Doctor Morrison to audit the hearing on 22 November with discretionary power to testify if he deems it necessary.

19. *Proposition 1-A*

Doctor Kilroy asked the Council whether or not it wished to take a position on Proposition 1-A, which will amend the State Constitution.

ACTION: Voted to support Proposition 1-A.

Mr. Hassard informed the Council that the official organization sponsoring 1-A had requested $5,000 financial support from CMA. Mr. Hassard said that historically CMA had not given monetary support to campaigns on non-health measures, and since this request fell into that category, he felt the request should be declined.

ACTION: Voted to decline request for financial support for Proposition 1-A.

20. *Medical Staff Survey Contract with SDPH*

Doctor Halter, chairman of the Commission on Hospital Affairs, asked approval of the Council for CMA (through the Committee on Medical Staff Surveys) to enter into a contract with the State Department of Public Health to survey the staffs of 72 non-accredited hospitals in the state on a consulting basis. He stated that the contract had not been submitted to the Committee in final form as yet, but wished the approval of the Council so that the Committee could act when the final contract was submitted. It was pointed out that the contract might include provision for channeling funds to compensate for the physician time involved to CMA, which would then reimburse the participating physicians on a per diem basis.

ACTION: Voted to approve entering into a contract with the State Department of Public Health to survey medical staffs on a consulting basis.

ACTION: Voted that in the event the contract is accepted, there should be included in it a provision for reimbursement, through CMA, of physician time.

21. *Effect on Utilization of Location of Extended Care Facilities*

The subject of the effect on utilization of location of extended care facilities was discussed. It was suggested that should a question on this subject arise, it might be referred to the Committee on Health Facilities Planning.

ACTION: Voted to refer questions on utilization, as it is related to the location of extended care facilities, directly to the Committee on Health Facilities Planning.

22. *Department of Mental Hygiene*

Doctor James Lowry distributed two publications to the Council for its information. One publication describes a new program for the mentally retarded begun last January with the combined efforts of the Department of Mental Hygiene and the Department of Rehabilitation. Patients who seem likely to be able to be returned to the community are selected for this program. The other publication describes changes in the inpatient population in mental hospitals. Doctor Lowry pointed out statistics showing that both the inpatient population and the admission rate continue to decrease.

23. *Stanford Medical School*

Dean Glaser informed the Council of the "Visiting Committee," initiated at Stanford one year ago, which visits the University twice a year and reviews the medical teaching programs. He said that the school had found this to be a useful tool in guiding their teaching programs.

Chairman Anderson thanked Dean Glaser for his kind letter to the Council expressing his appreciation for the opportunity to attend the meetings and report to the Council. Copies of the letter were distributed to the Council.

24. *University of California Medical Center, San Francisco*

Dean Cullen reported that Doctor Leslie L. Bennett, chairman of the Department of Physiology, had resigned to devote full time to his position as Vice Chancellor of Academic Affairs and that a new chairman for the department was being sought. He also informed the Council that UC is actively engaged in curricular changes to mesh with governmental health programs.

25. *University of California Medical School, Davis*

Dean Tupper announced that Doctor Hamilton Davis has joined the faculty at Davis as chairman of the Department of Anesthesiology. He was formerly with Western Reserve University. Doctor Tupper recently participated in an inspection team which did evaluation of a county medical society, on request, and made recommendations in such areas as postgraduate medical programs, internal administrative structure and economic policies. Doctor Tupper served on the team as the AMA physician. He also informed the Council that the Medical School at Davis was now formally affiliated with the Sacramento County Hospital.

26. *California Nurses' Association*

Mrs. Mary K. Stanley, president of the organization, informed the Council that the fact-finding panel appointed to look into the dispute between nurses and hospitals had made its recommendations and that these had been reviewed and accepted by both the nurses and hospital administrators. Mrs. Stanley also reported that nurses were concerned about the rising costs of hospitalization, but pointed out that in addition to nurses' salaries, such factors as hospital expansion, maintenance, and research also contribute to these rising costs. She said that the CNA had participated in the Health Manpower Council meeting in Santa Barbara, and that it hoped to be a permanent member of that Council.

27. *Woman's Auxiliary to the CMA*

Mrs. Dorothy Bacon, president, reported on the Woman's Auxiliary fall conference held recently. She said that noted speakers included Doctor Charles Hudson, president of the AMA, and Doctor James MacLaggan, CMA president, as well as the national Woman's Auxiliary President, and representatives of AMPAC and the Public Health League. Mrs. Bacon asked for any assistance physicians could give in helping the Auxiliary to recruit more members.

A letter and resolution of commendation to the CMA officers and others for their assistance to the Auxiliary during the past year was received by the Council.

28. *California Veterinary Medical Association*

Doctor Ben Dean, president of the Association, reviewed the one-day program that will be sponsored jointly by the CVMA and the CMA at the upcoming CMA Annual Session in Los Angeles. Among subjects to be discussed are emphysema, muscular dystrophy, leukemia, the use of radioactive isotopes in diagnosis and a cancer study.

29. *California Medical Assistants Association*

Mrs. Jeanette Gentile, immediate past president of the Association, introduced the new president, Mrs. Dorothy Fitzgerald, of Long Beach, to the Council.

30. *Medical Executives Conference*

Chairman Rueben Dalbec informed the Council that the Medical Executives Conference had appointed a committee to study meeting format and one progress report had already been submitted. He said that the Committee is still at work on format revision, and it was hoped that some specific recommendations would be presented to the Council for its approval at the next Council meeting.

31. *Health Manpower Council*

President MacLaggan presented background on the initiation of a Health Manpower Council and reviewed the Manpower Council meeting held recently in Santa Barbara. Two conclusions of that meeting were (a) that the Council should consist of 21 representatives: Three from CMA, three from CHA, one each from State Departments of Public Health, Employment and Education and one each from the nursing, nursing homes and dental organizations (leaving nine members unnamed, who will be chosen by the Hospital Advisory Council); and (b) that there should be a large yearly meeting called the Health Manpower Conference. Doctor MacLaggan asked that the Council formally approve CMA's participation in the Health Manpower Council and that three specific representatives be named.

ACTION: Voted to approve CMA actions to date and to establish CMA as an active member with representation at next planning meeting by Doctors MacLaggan, Morrison and Melone. Also voted to approve representation by the Woman's Auxiliary at the next Conference.

It was pointed out that CMA's membership in the Manpower Council would necessitate a monetary contribution, but no definite amount was proposed.

32. *Internships and Residencies for Graduates of Schools of Osteopathy*

Councilor Longmire informed the Council that the AMA Council on Medical Education had proposed a resolution that all approved internships and residencies should be made available to graduates of schools of osteopathy. He said that the resolution would come before the AMA Board of Trustees and probably would be introduced into the AMA House of Delegates. Doctor Longmire recommended that the CMA Council request that action on this proposal by the AMA Board of Trustees be deferred until after the AMA Las Vegas Meeting so that the CMA Council might have an opportunity to review it.

ACTION: Voted to request the AMA Board of Trustees to defer action on the proposed resolution.

33. *Office of Economic Opportunity*

Chairman Miller of the Commission on Public Agencies introduced to the Council Doctor Howard Lindsey, chairman of the CMA Committee on Welfare Medical Care Programs. Doctor Lindsey reported on the progress of the Committee as it is involved with the programs under the Economic Opportunity Act of 1964. He described the neighborhood health center programs and community action committees, which are the designated bodies for carrying out programs under the Act. The Council received a committee report which recommended that CMA establish close liaison with the State Office of Economic Opportunity, become a "repository" of information relating to Economic Opportunity projects, and stimulate liaison between local medical societies and Community Action Programs under OEO.

ACTION: Voted to grant authority to the Commission on Public Agencies to proceed with the recommended activities regarding the Economic Opportunity program.

34. *Defining "Lapses of Consciousness"*

For the information of the Council, it was reported that the question of definition of lapses of consciousness (California Administrative Code, Reportable Diseases and Conditions), which had been discussed at the previous Council meeting, passed the Board of Public Health exactly as it had been amended by the Council.

35. *Blue Shield—California Physicians' Service*

Richard S. Wilbur, chairman of the CPS Board, reviewed the status of Medicare and Medi-Cal claims, and said that CPS was receiving approximately 1,600,000 claims per month under both programs. Doctor Wilbur also informed the Council that Mr. Robert Koch had joined the staff of CPS as Executive Vice-President responsible to Mr. Thomas Paton, President. It was announced that a new *Physicians' Newsletter* would be issued soon describing the four CPS plans available to over 65 persons, either to round out their coverage in addition to Medicare, or for health care coverage in lieu of Medicare.

36. *Commission on Community Health Services*

Chairman Kay called attention to a "Health Tips" progress report and display and expressed special thanks to Mrs. Margaret Griffith and her assistant Miss Verna Holt for their work on this project.

Doctor Kay reported on the one-day conference on physicians for rural areas held 15 October in Los Angeles. He said that there were three representatives from each of six medical schools, and enumerated some productive suggestions resulting from the conference.

It was the recommendation of the Commission that the intent of House of Delegates Resolutions #83-66 (Poison Prevention) and #32-66 (Department of Motor Vehicles questionnaire) had been fulfilled and no further action was needed.

ACTION: Voted to approve the report of the Commission on the above resolutions.

Speaking for the Commission, Doctor Kay recommended that House of Delegates Resolution #51-66 (Motorcycle Safety) be referred to the Committee on Legislation for implementation.

ACTION: Voted to refer resolution #51-66 to the Committee on Legislation.

A resolution on increasing the staff of the Medical and Health Division of the California Disaster Office was presented to the Council for approval.

ACTION: Voted to approve the resolution.

37. *Scientific Board*

Chairman Longmire presented to the Council an "Outline Guide of Suggested Treatment of Persons Exposed to Rabies" submitted by the California State Department of Public Health. It was the recommendation of the Scientific Board that the "Outline Guide" be approved.

ACTION: Voted to approve the "Outline Guide of Suggested Treatment of Persons Exposed to Rabies."

Councilor Longmire reported that the Scientific Board again had recommended that money received by CMERF from Audio-Digest be given to California medical schools, divisions of continuing medical education (distributed equally among the schools).

ACTION: Voted to refer the recommendation of the Scientific Board to CMERF for consideration.

Doctor Longmire also reported that the Committee on Cancer proposed that a survey be made of the use of proctosigmoidoscopic examinations in California.

ACTION: Voted to approve the proposed survey in principle, with details to be submitted at a later date.

38. *Millis and Coggeshall Reports*

Doctor Edgar Wayburn proposed to the Council that an in-depth study of graduate medical education, including study and review of the Millis and Coggeshall reports, be referred to the Scientific Board.

ACTION: Voted to request the Scientific Board to study the Millis and Coggeshall reports, and report to the Council.

39. *Purpose of Committee on Organizational Review and Planning*

Past President Ralph Teall, chairman of the Committee on Organizational Review and Planning, submitted for Council approval the following proposed functions of his committee: (a) To review and define the objectives, goals and functions of the CMA; (b) to review and analyze problems in whose solution CMA should lead and participate; (c) to review the structural organization of CMA; and (d) to plan for and propose changes in CMA's organizational structure to improve its over-all functioning.

During discussion, Doctor Teall clarified priorities within the statement of purpose, saying that the Committee's activities for the current year would be primarily devoted to (a) and (b).

ACTION: Voted to approve the statement of purpose for the Committee on Organizational Review and Planning.

40. *Annual Statement of CMA Goals*

On behalf of the Committee on Organizational Review and Planning, Doctor Teall proposed that the Council annually establish goals for the CMA and request each Commission to do the same.

ACTION: Voted to prepare an annual broad statement of CMA objectives for presentation to the House of Delegates (Commissions also to review their goals annually).

41. *Conference with Representatives of Specialty Organizations*

The final recommendation of the Committee on Organizational Review and Planning was that CMA sponsor a conference with representatives of the many specialty organizations. Purpose of the conference was designated as being to seek to identify how the CMA and the specialty organizations can best work together by exploring differences and common interests.

ACTION: Voted to approve the concept of sponsoring a conference with representatives of specialty organizations and to request the Committee on Committees to submit suggestions for an appropriate conference steering committee.

42. *Membership*

Twenty-three applicants were voted election to Associate Membership. These were: Howard B. Flanders, Paul E. Morentz, Malcolm R. Powell, Miriam H. Rutherford, Ronald L. Thiele, Alameda-Contra Costa Counties; Thomas H. Horner, III, Imperial County; Margaret Bradley Blum, Harry Chao-Hung Fang, Frank M. Finck, Saul Goldberg, Frank Jay Haas, William Wood Lee, Ali Rachimogli Nijasi, W. Leslie G. Quinlivan, Ronald M. Reisner, Roger Melroy Shock, Frances P. Sheridan, William R. Simpson, Joseph David Teicher, Los Angeles County; Arthur M. Brandt, Parker Hollingsworth, Isadore Talesnick, Lydia L. Verbarg, Santa Clara County.

Eight members were voted election to Retired Membership. These were: Reinhard B. Lewis, Alameda-Contra Costa Counties; John C. McDermott, Vera C. Waegele, Howard E. Horner, Los Angeles County; Robertson Ward, Marin County; Jerome W. Bettman, Arno G. Folte, San Francisco County; Irving Wills, Santa Barbara County.

A reduction of dues was voted for 27 members for reasons of prolonged illness or postgraduate education.

43. *Roll Call*

Present were President MacLaggan, President-Elect Morrison, Speaker Quinn, Vice-Speaker Telford, Secretary Weyrauch, and Councilors Isenhour, Eastman, Melone, Todd, Gooel, Taw, Bullock, Ham, Rogers, Crum, Boyle, Burnett, Richard S. Wilbur, Miller, Watts, Fenlon, Kay, Kaiser, Anderson, Yant, Grunigen, Longmire, Immediate Past President Teall, and Acting Editor Wayburn. Absent for cause were Editor Dwight L. Wilbur and Councilors O'Connor and Maguire.

Present by invitation were CMA staff members Belser, Clark, E. Collins, J. Collins, Curley, Eberlein, Edwards, Goldman, Griffith, Hetland, Jones, Klutch, Lemos, Miller, Price, Redfern, Thomas, and Whelan; Messrs. Hassard and Huber, legal counsel; component society executives Scheuber of Alameda-Contra Costa, Brock of Imperial, Walters of Riverside, Dochterman of Sacramento, Donmyer of San Bernardino, Nute of San Diego, Neick of San Francisco, Wood of San Mateo, Marvin of Santa Barbara, Donovan of Santa Clara, Funk of Solano, Brown of Sonoma, and Bruce of Tulare; Messrs. Paton, Babb, Heller, Koch, Light, and Potloff of Blue Shield—California Physicians' Service; Messrs. Read, Brown, and Putnam of the Public Health League; Doctor Cullen of UC, San Francisco, School of Medicine; Doctor Glaser of Stanford School of Medicine; Doctors Bostick and Henley of UC, California College of Medicine; Doctor Tupper of UC, Davis, School of Medicine; Mr. Ward and Doctor Rosen of the Health and Welfare Agency; Doctor Lowry of the State Department of Mental Hygiene; Doctor Skelly of the State Department of Social Welfare; Mrs. Bacon of the Woman's Auxiliary to the CMA; Mrs. Stanley of the California Nurses' Association; Mrs. Fitzgerald of the California Medical Assistants Association; Doctor Dean of the California Veterinary Medical Association; Messrs. Gould and Gartland of the American Medical Association; Mr. Layton of the American Medical Political Action Committee; Doctors Davis, Halter, Kilroy, Lindsey, Ritter and others.

44. *Adjournment*

The meeting was adjourned at 4:35 p.m.

CARL E. ANDERSON, M.D., *Chairman*
HELEN B. WEYRAUCH, M.D., *Secretary*

CALIFORNIA MEDICAL ASSOCIATION

1967 ANNUAL SCIENTIFIC ASSEMBLY

Biltmore Hotel • Los Angeles • April 15-19

Plan NOW to Attend

Three General Sessions on

ADVANCES IN DIAGNOSTIC TECHNIQUE

DISTINGUISHED SPEAKERS INCLUDE:

- ★ William A. Altemeier, M.D., Chief, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati
- ★ Irvine H. Page, M.D., Director, Research Center, Cleveland Clinic, Cleveland
- ★ Herbert M. Stauffer, M.D., Professor and Chairman, Diagnostic Section, Department of Radiology, Temple University Science Center, Philadelphia
- ★ Jon V. Straumfjord, Jr., M.D., Professor and Chairman, Department of Clinical Pathology, Medical College, University of Alabama, Birmingham
- ★ George Zur Williams, M.D., Chief, Clinical Center, National Institutes of Health, Bethesda

SPECIAL CONFERENCES ON:

Cancer of the Colon and Rectum
Research Advances in Veterinary Medicine
The Impact of Medicare—Titles 18 and 19
Medicine and Religion—Moral Aspects of New Procedures

PLUS . . .

EIGHTEEN SCIENTIFIC SECTION PROGRAMS
SCIENTIFIC AND TECHNICAL EXHIBITS
COLOR TV AND FILM SYMPOSIA

L. HENRY GARLAND, M.D.

DR. L. HENRY GARLAND, secretary of the California Medical Association from 1946 to 1950, who long had served the association and the profession of medicine in many other capacities—scientific, legislative and administrative—died 31 October 1966 in San Francisco.

From his native Ireland where he had received his medical degree, Dr. Garland came to this country in 1926 to become resident in radiology at Stanford University Hospital, San Francisco. The year following completion of this residency, his application for membership in the California Medical Association was approved.

From his election in 1940 to the CMA House of Delegates as a representative of the San Francisco Medical Society, he was almost continuously active (with time out to serve as a commander in the U.S. Navy in World War II) in the affairs of this organization until the last months of his life. He was secretary of the CMA from 1946 until he resigned the post in 1950, and in that time he was also chairman of the Committee on Scientific Work. He was again elected to the House of Delegates in 1951 and was reelected year after year until 1962.

Dr. Garland was a member of the Cancer Commission of the Association (1946 to 1958) during a time of great progress in cancer research and therapy and of resounding investigations into quackery. At the same time he was on the board of directors of the California Division of the American Cancer Society from its inception in 1946 continuously until October 1963, and was vice president in 1948. He was secretary of the CMA Cancer Commission from 1952 to 1955; and from 1960 through 1965 he was a member of the Committee on New and Unproved Methods of Cancer Treatment of the CMA Commission on Cancer and of a successor committee which was formed in a reorganization of CMA committees.

Among his many positions in public service, Dr. Garland was a member of the Committee on Cancer Diagnosis and Therapy, National Research Council, from 1952 to 1957, serving as chairman for the last three years of the period. He was also a member of the Cancer Advisory Council, California State Department of Public Health, from 1959 on.

Dr. Garland was from its beginning a member of the California Medical Association's Scientific Board which was formed in 1963 to direct and coordinate all scientific programs of the Association. He was the first chairman of the Board's Committee on Scientific Information.

Concomitantly with his years of service to his state medical association, Dr. Garland was active in the practice and the teaching of radiology, a field in which he was internationally renowned and singularly honored. In California, as secretary of the California Radiological Society (previously Pacific Roentgen Society), he was for 32 years the leading figure in the medical-socioeconomic aspects of this specialty. In 1954 the Bronze Medal of the American Cancer Society was awarded to him for distinguished service, and in 1960 he received the Gold Medal of the American College of Radiology, of which he had been president. Almost from the time he completed his residency, he was a clinical teacher of radiology, first at Stanford (1929 to 1960) and then at the University of California, San Francisco, and for over 30 years chief of radiology at the San Francisco General Hospital.

Harry Garland had the sharp, bright, quick wit of his native land. He was a superb teacher and a consummate radiologist. Strong in his beliefs in the respective responsibilities of the individual citizen and the physician, he abhorred the intrusion of government into the practice of medicine. He set high standards for himself and could not tolerate lesser standards for others within or without the profession. His contributions to the CMA, to his students and residents and to his specialty were invaluable, highly individualistic and long lasting.

DWIGHT L. WILBUR, M.D.

In Memoriam

ALBRONDA, HENRY F., San Francisco. Died 30 October 1966, in San Francisco, aged 49, of coronary thrombosis. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1943. Licensed in California in 1943. Doctor Albronda was a member of the San Francisco Medical Society.

✣

BRAMKAMP, ROBERT GREENLEAF, San Bernardino. Died 14 September 1966, aged 61. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Doctor Bramkamp was a member of the San Bernardino County Medical Society.

✣

CALVY, LLOYD EDWARD, Orange. Died 13 October 1966, in Newport Beach, aged 42. Graduate of the University of Wisconsin Medical School, Madison, 1951. Licensed in California in 1952. Doctor Calvy was a member of the Orange County Medical Association.

✣

CLAYTON, JAMES O., Redondo Beach. Died 21 June 1966, in Culver City, aged 76, of congestive heart failure, renal failure, and arteriosclerotic heart disease. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1932. Licensed in California in 1935. Doctor Clayton was a member of the Orange County Medical Association.

✣

DAVIS, HAROLD LEROY, Sunnyvale. Died 23 October 1966, in Tiajuana, Mexico, aged 47, of heart disease. Graduate of the University of Nebraska College of Medicine, Omaha, 1951. Licensed in California in 1955. Doctor Davis was a member of the Santa Clara County Medical Society.

✣

DAYTON, GLENN ORVILLE, SR., Los Angeles. Died 23 October 1966, in Los Angeles, aged 85, of cerebral thrombosis. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1907. Licensed in California in 1921. Doctor Dayton was a member of the Los Angeles County Medical Association.

✣

FRICKE, ALBERT ADOLPH, Los Angeles. Died 7 October 1966, in Los Angeles, aged 87, of arteriosclerotic heart disease. Graduate of the University of Nebraska College of Medicine, Omaha, 1908. Licensed in California in 1920. Doctor Fricke was a member of the Los Angeles County Medical Association.

✣

GALLAS, DIGBY, Los Angeles. Died 10 October 1966, in Inglewood, aged 59. Graduate of Marquette University School of Medicine, Milwaukee, Wisconsin, 1944. Licensed in California in 1948. Doctor Gallas was a member of the Los Angeles County Medical Association.

GARLAND, L. HENRY, San Francisco. Died 31 October 1966, in San Francisco, aged 63. Graduate of the University College of Dublin, Ireland, 1924. Licensed in California in 1925. Doctor Garland was a member of the San Francisco Medical Society.

✣

GITTLEMAN, BEN, Los Angeles. Died 23 October 1966, in Los Angeles, aged 57, of carcinoma. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1933. Licensed in California in 1933. M.D. degree from California College of Medicine, 1962. Doctor Gittleman was a member of the Los Angeles County Medical Association.

✣

HENRY, BOYD D., Los Angeles. Died 27 September 1966, aged 59. Graduate of Kirksville College of Osteopathy and Surgeons, Missouri, 1929, and the College of Osteopathic Physicians and Surgeons, Los Angeles, 1948. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Doctor Henry was a member of the Los Angeles County Medical Association.

✣

ILLICK, CHARLES RAYMOND, Santa Paula. Died 24 September 1966, in Oxnard, aged 80. Graduate of Wayne University College of Medicine, Detroit, Michigan, 1919. Licensed in California in 1928. Doctor Illick was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

LACOE, JEREMIAH RALPH, Los Angeles. Died 22 October 1966, in Los Angeles, aged 64, of cerebral vascular accident. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1927. Licensed in California in 1928. Doctor Lacoe was a member of the Los Angeles County Medical Association.

✣

LENERT, CHARLES, Sacramento. Died 26 October 1966, in Sacramento, aged 50. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1944. Licensed in California in 1945. Doctor Lenert was a member of the Sacramento County Medical Society.

✣

LINDSAY, WILLIAM W., San Francisco. Died 21 June 1966, aged 47. Graduate of New York Medical College, Flower and Fifth Avenue Hospitals, New York, 1943. Licensed in California in 1952. Doctor Lindsay was an associate member of the San Francisco Medical Society.

✣

OSBORNE, ROLAND HARRIS, Santa Monica. Died 29 October 1966, in Los Angeles, aged 66, of cancer of the liver. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Doctor Osborne was a member of the Los Angeles County Medical Association.

PETCH, PHILIP HENRY, Oakland. Died 20 October 1966, in Oakland, aged 79, of myocardial failure. Graduate of Cooper Medical College, San Francisco, 1909. Licensed in California in 1909. Doctor Petch was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

RANSOM, JACK KENNEDY, Modesto. Died 26 June 1966, aged 83, of bronchopneumonia. Graduate of Cooper Medical College, San Francisco, 1910. Licensed in California in 1910. Doctor Ransom was a retired member of the Stanislaus County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

REES, CHARLES W., San Diego. Died 9 October 1966, in Mission Hills, aged 66. Graduate of New York University College of Medicine, New York, 1926. Licensed in California in 1930. Doctor Rees was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

ROBERTSON, DONALD LOGAN, Modesto. Died 27 October 1966, in Modesto, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Doctor Robertson was a retired member of the Stanislaus County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

ROSENFELD, MAURICE H., Los Angeles. Died 24 October 1966, in Los Angeles, aged 67, of metastatic carcinoma of colon. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1924. Licensed in California in 1930. Doctor Rosenfeld was a member of the Los Angeles County Medical Association.

SMITH, GIBSON CARR, San Diego. Died 22 September 1966, in San Diego, aged 49, of heart disease. Graduate of the University of Wisconsin Medical School, Madison, 1944. Licensed in California in 1952. Doctor Smith was a member of the San Diego County Medical Society.

⁂

STEEN, CLAUDE EARL, Fullerton. Died 23 August 1966, aged 74. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1918. Licensed in California in 1918. Doctor Steen was a member of the Orange County Medical Association.

⁂

SURACI, ROCCO T., Oakland. Died 2 November 1966, aged 53. Graduate of Marquette University School of Medicine, Milwaukee, 1940. Licensed in California in 1940. Doctor Suraci was a member of the Alameda-Contra Costa Medical Association.

⁂

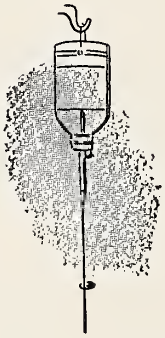
SVOBODA, FRANK CHARLES, San Diego. Died 7 October 1966, aged 67. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1925. Licensed in California in 1926. Doctor Svoboda was a member of the San Diego County Medical Society.

⁂

VAN COTT, WESLEY BAILEY, Los Angeles. Died 20 October 1966, in Salt Lake City, Utah, aged 61. Graduate of Northwestern University Medical School, Chicago, Illinois, 1930. Licensed in California in 1931. Doctor Van Cott was a member of the Los Angeles County Medical Association.

⁂

WILKINSON, HENRY FIELDING, San Gabriel. Died 12 August 1966, in San Gabriel, aged 70, of emphysema. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1921. Licensed in California in 1936. Doctor Wilkinson was an associate member of the Los Angeles County Medical Association.



application for HOTEL ACCOMMODATIONS

NINETY-SIXTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • APRIL 15-19, 1967

BILTMORE HOTEL, LOS ANGELES

House of Delegates Opening Session Saturday evening, April 15; Scientific Programs begin Sunday morning, April 16.

1. Fill in the form below **completely** for room accommodations at the CMA's 1967 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, 693 Sutter Street, San Francisco, California 94102.
4. **DEADLINE** for housing: April 1, 1967.

HOTEL ROOM RATES*

	Single	Double and Twins	Suites
BILTMORE HOTEL			
515 So. Olive Street	10.50-17.50	15.50-21.50	30.00-55.00
MAYFLOWER HOTEL			Triples
535 So. Grand Avenue	8.50-13.50	12.00-17.50	22.00
STATLER-HILTON			Suites
930 Wilshire Boulevard	11.00-17.50	16.00-22.50	30.00-65.00

*Rates subject to change

Send to: California Medical Association—*Housing Bureau*
693 Sutter Street, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1967 Annual Session in Los Angeles, April 16-19, 1967. The first meeting of the House of Delegates begins Saturday evening, April 15; Scientific Programs begin April 16.

Single Bedroom $.................................Twin-Bedded Room $.................................Double Bedroom $.......................

Small Suite $..Large Suite $..Other $..................................

First Choice Hotel..Second..

Arrival (date) ....Hours........................a.m. p.m. Departure (date) ....Hour........................a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of both persons for each twin-bedded or double room, and names and addresses of all other persons for whom you are requesting reservations.

....

....

....

....

—PLEASE PRINT—

Your Name ....Officer? .... Delegate? .... Alternate? .... Speaker? ....

Address .... County ....

City and State..Zip No. ....

Continuing Medical Education for the Practicing Physician

THOMAS B. TURNER, M.D., *Baltimore*

NEITHER THE FACT OF continuing education for the practicing physician nor the need for it is new, only the mechanisms for implementing such continuing education are new. Some of the modern means of communication offer great potentials for keeping the practicing physician abreast of the advances in medicine. Indeed, we may envision a wholly new dimension to medical education.

No one educational pattern is likely to be used exclusively. Nor should responsibility for continuing education of the physician rest solely on any one organization or professional group. Nevertheless, education is the special task of the university, and it is to this source that we should look for leadership.

It is appropriate, therefore, for the Association of American Medical Colleges to be deeply concerned about the proper role of the medical school in this large new area of medical education. The risk is that the Association and the medical schools will do too little, not that they will do too much in this field.

Two problems, obviously related to one another, emerge. The one is how to discover the most effective ways of continuing the lifelong educational process begun within the walls of the medical school. The other is how to create incentives, aside from the natural desire for knowledge, that will encourage the physician to continue his education.

If postdoctoral medical education is viewed in its entirety, two fairly well defined periods can be identified. One is the immediate postdoctoral period up to the point of certification as a specialist; the other is the period beyond certification. Parenthetically, I believe that all practitioners of the future will be specialists, among the most important specialty being that of the personal physician. In this article I shall comment principally on the second and more difficult educational activity, which can be referred to as continuing medical education.

My own background leads me to hold that the medical schools of the country should be the focal points of this extramural educational program, primarily because medical education is their business; but also because many of the things the medical schools are already doing can be readily modified and further developed to meet this need. For example, most clinical departments of medical schools hold at some point in the week so-called grand rounds at which unusual cases and vexing clinical problems are presented and discussed. These are held at fixed locations, necessitating travel of the practicing physician to them, the sessions are often held at times that are not convenient to the practitioner, and the subject matter is inclined to deal with the unusual and thereby hold less immediate appeal to the man in private practice.

None of these objections, however, seems to embody a fatal weakness. True, the audience that such an activity can reach is limited geographically, although some of our own sessions in Baltimore draw from a radius of upwards of a hundred miles. Scheduling of the teaching sessions on Saturday mornings or on a fixed afternoon during the week has proved to be reasonably satisfactory to many. With reference to the selection of cases for presentation, there is something to be said for use of the problem case, for often the unusual in medicine today is the commonplace tomorrow.

A variation on this pattern has been a series of six to 10 weekly sessions at some point during the year, termed Clinical Thursdays (or whatever the day may be) in which practitioners within motoring distance spend the entire day at the medical school in various types of clinically oriented sessions.

But clearly, the activities just referred to can at most reach only those physicians who are practicing within a reasonable radius of the university medical center. How is it possible to develop an educational process that will reach the larger proportion of physicians not so situated? The answers

---

For ten years Dr. Turner has been Dean of the Medical Faculty of The Johns Hopkins University School of Medicine, and he is the immediate Past President of the Association of American Medical Colleges.

This article was prepared especially for CALIFORNIA MEDICINE at the request of the Committee on Continuing Medical Education of the California Medical Association.

would seem to lie along two lines which can be best developed together: Imaginative use of modern communications particularly closed-circuit television, and establishment of a network of educational centers as satellites of the university-based medical school. The recently inaugurated federal program directed to heart, cancer and stroke should materially accelerate the development of such activities.

We must here pause to consider some basic educational problems. Of first importance is the fact that the individual must want further education and must be prepared to expend effort to get it if education is to be effective. Second, some importance must be placed on good teaching, which includes thoughtful preparation and personable presentation; theoretically at least the best teachers should be found in medical schools. Third, there is merit in group reception and group discussion, and emphasis should be placed on bringing physicians together in some formal fashion where the interplay of knowledge and skills can be felt, rather than relying upon television piped into the physician's home or office. Finally, there should be some method of evaluating the results of this educational effort and probably some reward implicit or explicit to the physician who expends the effort to improve himself professionally.

To be specific, and I hope practical, I would visualize a network of university-affiliated hospitals stretching across the country, each an educational institution in a small way and each in close intellectual contact with its own university medical center through closed-circuit television, exchange of professional staff including house staff, and ready availability of scarce specialty consultants. Such satellites can be established without the parent institution in any way exercising control over the affiliated hospital or interfering in any substantive way with the professional care activities in those institutions. Such affiliated hospitals might, in turn, have their own sub-affiliates.

Valuable experience has already been obtained in the use of radio and television in a number of states, notably New York, Kansas, California and Maryland, where either the state health departments or the state medical societies have sponsored continuing medical education programs. That they have had only limited success is, in my opinion, principally due to lack of a firm medical school base for the activity.

This raises an important question, which is whether in fact the medical schools are willing to undertake such programs as an integral and vital part of their educational responsibility. Naturally I cannot speak for the medical faculties of the country on this point, but it is my opinion that they should assume this obligation, provided the activity can be properly financed; although such programs will not be highly effective unless the institutions are persuaded of the importance of this phase of medical education.

Finally, what about incentives that will encourage physicians to improve their professional knowledge and skills? The thought of periodic examinations or testings is abhorent to those of us who struggled so hard to qualify in the first place. On the other hand, it does not seem unreasonable to develop some kind of check-point in mid-career that would establish a continuing right to specialty categorization. This is an area fraught with controversial issues, but the problem will not go away by simply ignoring it. It will probably be wise to approach it as an educational problem to be dealt with in an educational context, rather than through licensing devices.

Two American organizations, the Association of American Medical Colleges and the Council on Medical Education of the American Medical Association, for over half a century have acted jointly in promoting high standards of medical education; it is to these two organizations that we should look for leadership in reemphasizing the importance of postdoctoral education.

Whither Continuing Medical Education?

DONALD W. PETIT, M.D., *Los Angeles*
Chairman, Committee on Continuing Medical Education

THE ESCALATION of government's role in health care has greatly increased the efforts to establish standards of health care and standards of educational course merit. Such yardsticks are being devised in many ways: Questionnaires are being sent to physicians, to educators—at times even to patients—in an effort to find out "What is a good doctor?" As yet, the results have been unsatisfactory, but the search goes on. Similarly, studies of postgraduate teaching techniques are now developing, to try and decide if a course is good—does the participant take any of this material to his practice?

The search for answers to these questions is motivated largely by a desire to improve patient care. If somehow a template could be designed that evaluated the performance of a physician's work, then all present and future physicians could be so tailored and periodically retailored. Similarly, all postgraduate courses could be designed to meet not only a standard of predetermined excellence, but also to reflect the actual needs and demands of physicians, as perceived both by doctors and educators alike.

The Committee on Continuing Medical Education of the California Medical Association is deeply concerned with these problems. The concern, however, reflects a desire to encourage individuality of learning by the practicing physician and to encourage regular recurring participation in educational activities by all physicians, not just a portion of them. The concern also reflects a desire that no blanket of uniformity be cast over teacher and student alike, with all fitting the same Procrustean bed.

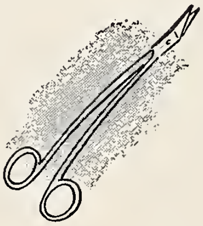
Somewhere between the chaos and regression of self satisfied no-education and the rigidity of externally imposed standards must be a better way. To determine this, it will be necessary to obtain in a factual way the true extent of participation by practicing physicians now in their own continuing education. The California Medical Association plans to inventory courses and identify their characteristics in order that a comprehensive record may be developed to provide detailed information for the medical profession. The definition of continuing education will somehow have to be broadened to include not only organized courses and conferences of different types, but also time on teaching services, outpatient clinics and journal clubs, to mention a few. Any time that physicians come together to discuss medical problems is an exercise in continuing education. The attending physician on a ward service, for example, is receiving postgraduate education.

When the extent of these activities is known, then the entire structure of continuing education can be approached with the goal of increasing participation in these activities to the point that it can be said truthfully that all of our physicians are engaged in learning and that they continue to be so engaged. The physician who exposes himself to and regularly participates in continuing educational exercises is the good doctor, almost by definition. An attempt to assay a physician's worth by the way he fills out a record or by the technique he uses for a particular procedure, seems inflexible, and eventually the road to perpetuation of errors and stagnation of learning.

Medical educators should be encouraged to develop their own methods and techniques of teaching and allowed the freedom to experiment with new and, hopefully, more effective teaching programs.

The next few years will see developments in California designed to allow experimentation in teaching and learning techniques. These will range from trials of automated teaching machines at regional conferences to pilot programs for in-hospital residency-type continuing education programs. This latter could well, but not necessarily, be a time of temporary separation from practice and full time devotion to learning new skills and approaches.

We, as physicians, are under the greatest pressure to keep up with new knowledge. The efforts that are being expended at present and those which will evolve in the future, will enable us to determine to what extent we are fulfilling our obligations as members of our profession, and the expectations of the patients and public we serve.



NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. George J. Hummer, Santa Monica, was elected president-elect of the American Association of Blood Banks at the recent convention of the organization in Los Angeles. Mrs. Bernice M. Hemphill, managing director of the Irwin Memorial Blood Bank, San Francisco, was reelected treasurer of the association.

* * *

Dr. Steven Lee, a third-year resident in pathology at Cedars-Sinai Medical Center, is recipient of a $1,000 Warner-Chilcott Fellowship, one of two awarded nationally this year by the **American Society of Clinical Pathologists.** The award is aimed at fostering high standards in clinical pathology and encouraging outstanding pathology residents with potential teaching ability to enter the field.

Dr. Lee is a graduate of the University of California, Berkeley. He received his medical degree at the University of California, San Francisco. He is also a clinical associate in pathology at the California College of Medicine, Los Angeles.

* * *

Two-year fellowships in pulmonary disease and applied physiology, with option for a third year, are being offered by the University of Southern California School of Medicine and the Los Angeles County General Hospital for physicians intending to enter private practice or academic medicine. Stipends are $7,500 the first year, $8,500 the second and $9,500 the third. Two years of residency in internal medicine in an approved hospital or its equivalent, and United States citizenship or a permanent visa, are required. This training program affords an opportunity for broad clinical and diagnostic, laboratory, and investigative experience in thoracic medicine. Fundamental aspects of environmental medicine and air pollution, and relationship to pulmonary disease will be emphasized.

Further information may be obtained from Clayton G. Loosli, M.D., Ph.D., Program Director, University of Southern California, School of Medicine, 2025 Zonal Ave., Los Angeles 90033.

* * *

A Department of Community Medicine and Public Health has been established at the University of Southern California School of Medicine under a $375,000 grant from The Commonwealth Fund, it was announced today by Dr. Roger O. Egeberg, dean.

Dr. Robert E. Tranquada, associate professor of medicine, is chairman of the new department, which is intended to extend the School's activity in effective health-care organization and delivery at the community level.

The broad function of the department will be to close the gap between modern medical knowledge and the application of that knowledge in patient care.

GENERAL

The California Medical Education and Research Foundation, a nonprofit organization of the California Medical Association, will serve as the fiscal agent for a grant of $223,400 by the National Institutes of Health to be used for planning regional medical programs **to improve the diagnosis and treatment of heart disease, cancer, stroke, and related diseases.**

The grant was made to the California Committee on Regional Medical Programs, a statewide voluntary committee formed to assist medical schools and hospitals in the development of cooperative medical programs under new federal legislation. The grant is the first for a projected three years of planning. Succeeding grants are expected to bring the total to about $650,000.

The officers of the California committee are: Chairman, **Dr. Robert J. Glaser,** vice president for medical affairs and dean of the Stanford University School of Medicine; vice chairman, **Dr. Ralph C. Teall,** past president of the California Medical Association; secretary-treasurer, **Mr. Mark Berke,** past president of California Hospital Association.

Some of the planning studies will be conducted by a full-time staff to be employed and located in San Francisco, Dr. Glaser said. Other studies and planning activities will be carried out by the various medical schools, the California Medical Association, California Hospital Association, California State Department of Public Health and other health agencies.

INDEX

California Medicine

Volume 105

July-December 1966

AUTHOR INDEX

PAGE

A

Adams, Forrest H., *Los Angeles* 11
Adams, Joel E., *San Bernardino* 22
Alcocer, Arthur E., *Berkeley* 290
Allen, J. Garrott, *Palo Alto* 147
Anderson, Bruce M., *Oakland* 307
Anderson, Ramona, *Sacramento* 429

B

Bailey, Byron J., *Torrance* 271
Bartz, Albert F., *Hayward* 124
Bateman, Joseph R., *Los Angeles* 440
Bates, Talcott, *Monterey* 81
Bernstein, Harold, *Beverly Hills* 440
Beutler, Ernest, *Duarte* 440
Blejer, Hector P., *Los Angeles* 290
Blumenfeld, Charles M., *Sacramento* 429
Boland, Edward W., *Los Angeles* 249
Brayton, Donald, *Los Angeles* 237
Breslow, Lester, *Berkeley* 64
Brooks, Bobbie J., *San Diego* 171

C

Cann, John E., *San Francisco* 361
Caplan, Paul E., Los Angeles 290
Cardozo, Douglas W., *Santa Rosa* 210
Carlsen, Ray A., *Palo Alto* 415
Carpenter, Charles M., *Los Angeles* 167
Chen, Irene, *El Centro* 210
Chinnock, Robert F., *Loma Linda* 81
Clark, P. L., III, *Downey* 219
Claud, Phillips L., *El Centro* 210
Coblentz, David R., *Los Angeles* 357
Corsa, Leslie, Jr., *Berkeley* 81
Crossland, Paul, *Santa Rosa* 164
Cunningham, George C., *Berkeley* 1

D

Davis, James E., *Inglewood* 421
Day, Robert W., *Berkeley* 50
DeFalco, Alfred J., *Rochester, N. Y.* 93
Dillon, John B., *Los Angeles* 159
DuBois, James J., *San Francisco* 379
Dunn, James M., *Oakland* 125
Dunn, John E., Jr., *Berkeley* 331

E

Eisenberg, Robert S., *Altadena* 214
Ellis, Joseph G., *San Diego* 435
Epstein, Ervin, *Oakland* 26
Escamilla, Roberto F., *San Francisco* 104

F

Faber, Harold K., *San Francisco* 228
Farber, Eugene M., *Palo Alto* 415
Finkle, Alex L., *San Francisco* 66
Forsham, Peter, *San Francisco* 104
Fyler, Donald C., *Los Angeles* 11

G

Garland, L. Henry, *San Francisco* 8
Garrett, Alice L., *Downey* 219
Gerber, Alex, *Alhambra* 377
Gilbert, Arnold, *Berkeley* 81
Griffith, George C., *Los Angeles* 11
Gunther, Ronald E., *Palo Alto* 424

H

Harer, W. Benson, Jr., *Rialto* 424
Hastings, Newlin, *Los Angeles* 35
Hayashida, Takeshi, *Downey* 219
Haycraft, Rexford G., *Offut Air Force Base, Neb.* 89
Hayman, Max, *Los Angeles* 117
Herman, Irvin, *Oakland* 287
Hodgman, Joan E., *Los Angeles* 454
Hutchings, John J., *San Francisco* 104
Hutchinson, John C., *San Francisco* 352
Hyman, Carol B., *Los Angeles* 81

J

Jacobson, Yorke G., *New York City* 93
Jennings, E. R., *Long Beach* 146
Johnson, James R., *Los Angeles* 111
Johnstone, Rutherford T., *Los Angeles* 262

K

Keller, Melvin, *Baltimore* 93
Klein, Arvin J., *San Diego* 171
Knott, Margaret, *Vallejo* 179
Konya, Izabella O., *Los Angeles* 167
Kuchar, Benjamin E., *Torrance* 182
Kushner, Joseph H., *San Francisco* 81
Kuzman, William J., *San Diego* 171, 435

L

Le Clair, Ronald A., *Los Angeles* 167
Lewis, Arline, *Berkeley* 81
Lewis, Martin I., *Los Angeles* 457
Li, Choh Hao, *San Francisco* 104
Linden, George, *Berkeley* 331
Loeffler, Alan B., *Escondido* 265

M

Madoff, Lawrence, *Oakland* 208
Mahoney, Paul S., *San Fernando* 381
Marmor, Leonard, *Los Angeles* 28

KEY TO ABBREVIATIONS USED

(BRP)—Bureau of Research and Planning; (CMA)—California Medical Association; (CR)—Case Report; (CS)—Cancer Studies; (Ed.)—Editorial; (I)—Information; (LE)—Letter to Editor; (MSC)—Medical Staff Conference; (Or.)—Original Article; (PE)—Page End; (RSB)—Report of Scientific Board.

Masters, Harold, *Beverly Hills* 440
McClenethan, James E., *Washington, D. C.* 93
Mead, Sedgwick, *Vallejo* 179
Mundth, Eldred D., *Boston* 93

N

Nahum, Alan M., *Los Angeles* 271
Nelson, Leslie G., *Los Angeles* 454

O

Oatway, William H., Jr., *Altadena* 214
Overstreet, Edmund W., *San Francisco* 337

P

Pait, Charles F., *Los Angeles* 11
Palmer, J. J., *Los Angeles* 146
Payne, John R., *Woodland* 281
Petit, Donald W., *Los Angeles* 485
Phibbs, Roderic H., *San Francisco* 442
Pinto, Douglas, *San Francisco* 97
Pops, Martin A., *Los Angeles* 201, 420

R

Raskind, Robert, *Oakland* 125
Regan, James F., *Los Angeles* 457
Rivin, Arthur U., *Los Angeles* 102
Roe, Benson B., *San Francisco* 352
Rubaum, Norman, *Alhambra* 377

S

Schaupp, Karl L., Jr., *San Francisco* 97
Schleissner, L. A., *Torrance* 41
Schneidman, Harold M., *San Francisco* 368
Sheehy, James L., *Los Angeles* 31
Sherwin, Lawrence, *San Francisco* 337
Shuler, Stanton E., *New Orleans, Louisiana* 113
Siegel, Earl, *Chapel Hill, North Carolina* 81
Smith, William M., *San Francisco* 371
Solomon, Joel, *Duarte* 440
Sperling, Donald R., *Los Angeles* 340
Stoike, Roger D., *San Diego* 171
Sudrann, Robert, *Sacramento* 38

T

Teicher, Joseph D., *Los Angeles* 18
Tesluk, Henry, *Sacramento* 38
Thurlow, Alfred A., Jr., *Santa Rosa* 210
Turner, Thomas W., *Baltimore* 484

V

Valentine, Rodney J., *San Francisco* 97
Verska, Joseph J., *Los Angeles* 340

W

Wahl, Charles William, *Los Angeles* 276
Walch, Henry, *San Diego* 265
Walike, Barbara, *Los Angeles* 28
Wallace, Mary Jean, *Sacramento* 429
Waller, Julian A., *Berkeley* 197
Weinstein, Eugene C., *Downey* 219
West, Irma, *Berkeley* 257
Whiting, Edward G., Jr., *San Francisco* 284
Wiita, Robert M., *Jasper, Alabama* 265
Wilson, Edwin S., Jr., *San Francisco* 284, 379
Wright, Harry T., *Los Angeles* 345
Wyborney, V. J., *San Diego* 265
Wycoff, Charles C., *San Francisco* 361

SUBJECT INDEX

A

Abdominal Pain (MSC), see *Hyperlipemia*
Abortion, Induced, see *Hyperbaric Oxygen*
Abortion, Therapeutic, Attitudes and Practices of California Physicians, Lawrence Sherwin and Edmund W. Overstreet (Or.) 337
Accidents, Traffic, Chronic Medical Conditions as a Cause, Julian A. Waller (Or.) 197
Achondroplastic Dwarfism—Effects of Treatment with Human Growth Hormone, Roberto F. Escamilla, John J. Hutchings, Choh Hao Li and Peter Forsham (Or.) 104
Acid Phosphatases, Deceptive—Letter to Editor, Alex L. Finkle (LE) 66
Acute Cadmium Fume Poisoning in Welders—A Fatal and a Nonfatal Case in California, Hector P. Blejer, Paul E. Caplan and Arthur E. Alcocer (CR) 290
Adenomatous Polyp, Benign, see *Primary Duodenal Carcinoma*
Adolescents, Group Psychotherapy with, Joseph D. Teicher (Or.) 18
Advances in the Theory and Practice of Exchange Transfusions, Roderic H. Phibbs (Or.) 442
Alcoholism, Methods in Therapy in, Max Hayman (Or.) 117
Anemia, Hemolytic, see *Congenital Toxoplasmosis*
Anesthesia, Caudal, see *Long Acting Single Injection*
Anesthesia, Spinal, see *Rational Basis for*
Anesthetic and Recovery Room Records, John B. Dillon (Or.) 159
Angiosarcoma of the Scalp, see *Cystic Pulmonary Metastasis*
Aortic Homograft, Rupture, see *Gastrointestinal Hemorrhage*
Arachnidism, Necrotic, Martin I. Lewis and James F. Regan (Or.) 457
Arthritis, Gouty, see *Gout*
Asthma, Tokyo-Yokohama, A Review and Some Current Concepts, Rexford G. Haycraft (Or.) 89

B

Benign Adenomatous Polyp, see *Primary Duodenal Carcinoma*
Bovine Bile Derivative Treatment for Cancer—A Critical Evaluation, Harold Masters, Joel Solomon, Joseph R. Bateman, Harold Bernstein, and Ernest Beutler (Or.) 440

C

Cadmium Fume Poisoning, see *Acute Cadmium Fume Poisoning*
California Tumor Registry Reports, 1942-1963, see *Earlier Diagnosis of Cervical Cancer*
Cancer, see *Bovine Bile Derivative Treatment*
Cancer, Cervical, see *Earlier Diagnosis*
Cancer, Lung, see *Primary Lung Cancer*
Cancer of the Larynx—Results of Surgical and Radiological Treatment in One Institution, L. Henry Garland (Or.) 8
Carcinoma, Primary Duodenal, Antedated by a Benign Adenomatous Polyp, Edwin S. Wilson, Jr. and James J. DuBois (CR) 379
Carbocaine® (Mepivacaine), see *Long Acting Single Injection*
Cardiac Valve Replacement in Patients Over Sixty—A Report of Ten Operations with One Death, Benson B. Roe and John C. Hutchinson (Or.) 352
Cardiovascular Manifestations and Surgical Therapy in Infants, see *Rubella Syndrome*
Cardioversion, Electrical, Effectiveness of Quinidine Prophylaxis Following Countershock, Arvin J.

Klein, William J. Kuzman, Roger D. Stoike and Bobbie J. Brooks (Or.) ... 171

Caudal Anesthesia, see *Long Acting Single Injection*

Cervical Cancer, see *Earlier Diagnosis of*

Childhood, Psoriasis in, Eugene M. Farber and Ray A. Carlsen (Or.) ... 415

Chronic Renal Failure, Management of (MSC) ... 45

Chronically Draining Ear, The—Notes on Management in the Office, James L. Sheehy (Or.) ... 31

Circulatory Disorders of the Lower Extremities, see *Treatment*

Clinically Severe Lactic Acidosis with Coma, John R. Payne (CR) ... 281

Coma, Prolonged, see *Glutethimide Intoxication*

Congenital Anomalies and Viral Infections in Infants—The Etiologic Role of Maternal Viral Infections, Harry T. Wright, Jr. (Or.) ... 345

Congenital Skull Fracture, James M. Dunn and Robert Raskind (CR) ... 125

Congenital Toxoplasmosis with Hemolytic Anemia, Leslie G. Nelson and Joan E. Hodgman (CR) ... 454

Constitutional Amendments, Proposed, for Action in 1967 (CMA) ... 401

Continuing Medical Education:
  Television—Newest Medium for Continuing Education in Medicine, Donald Brayton (CMA) ... 237

Continuing Medical Education for the Practicing Physician, Thomas B. Turner (CMA) ... 484

Continuing Medical Education, Whither? Donald W. Petit (CMA) ... 485

Contraceptive Device, Intrauterine, see *Term Twin Pregnancy with*

Control of Post-Transfusion Hepatitis, E. R. Jennings and J. J. Palmer (LE) ... 146
  Reply by author, J. Garrott Allen ... 147

County/Teaching Hospitals—Statement of the CMA Council (I) ... 74

Cryotherapy, Topical, Use for Relief of Pain and Spasticity, Sedgwick Mead and Margaret Knott (Or.) ... 179

Cystic Pulmonary Metastasis Complicating Angiosarcoma of the Scalp, Douglas W. Cardozo, Phillips L. Claud, Irene Chen and Alfred A. Thurlow, Jr. (CR) ... 210

Cysticercosis (MSC) ... 463

D

Deceptive Acid Phosphatases, Letter to Editor, Alex L. Finkle (LE) ... 66

Dermatologic Therapy—Point and Counterpoint, Paul M. Crossland (Or.) ... 164

Differentiation of Dysfunction from Rupture of Papillary Muscle, Robert Sudrann and Henry Tesluk (CR) ... 38

Dimethyl Sulfoxide, Experience with, Leonard Marmor and Barbara Walike (Or.) ... 28

Disseminated Tuberculosis of Bone, Edwin S. Wilson, Jr. and Edward G. Whiting, Jr. (CR) ... 284

Duodenal Carcinoma, see *Primary*

Dwarfism, see *Achondroplastic*

Dysfunction, Differentiation of, from Rupture of Papillary Muscle, Robert Sudrann and Henry Tesluk (CR) ... 38

E

Ear, Chronically Draining, Notes on Management in the Office, James L. Sheehy (Or.) ... 31

Earlier Diagnosis of Cervical Cancer—An Analysis of Reports to the California Tumor Registry from 1942 to 1963, George Linden and John E. Dunn, Jr. (Or.) ... 331

Electrical Cardioversion—Effectiveness of Quinidine Prophylaxis Following Countershock, Arvin J. Klein, William J. Kuzman, Roger D. Stoike and Bobbie J. Brooks (Or.) ... 171

Exchange Transfusions, Advances in Theory and Practice, Roderick H. Phibbs (Or.) ... 442

Exophthalmos, Malignant (MSC) ... 222

Experience with Dimethyl Sulfoxide, Leonard Marmor and Barbara Walike (Or.) ... 28

Experimental Pulmonary Air Embolism in Dogs, Charles C. Wycoff and John E. Cann (Or.) ... 361

F

Fever, Rheumatic, see *Rheumatic Fever*

G

Gas Gangrene Following Induced Abortion, see *Hyperbaric Oxygen—(Therapy)*

Gastroenteropathy, Protein Losing, Martin A. Pops (Or.) ... 201, 420

Gastrointestinal Hemorrhage Due to Rupture of an Aortic Homograft, Alex Gerber and Norman Rubaum (CR) ... 377

Glutethimide Intoxication with Prolonged Coma and Hyperpyrexia Treated with Methylphenidate, L. A. Schleissner (CR) ... 41

Gout and Gouty Arthritis—Current Concepts and Management, Edward W. Boland (Or.) ... 249

Group Psychotherapy with Adolescents, Joseph D. Teicher (Or.) ... 18

Growth Hormone, see *Achondroplastic Dwarfism*

Growth Retardation (MSC), see *Hyperlipemia*

Guthrie (PKU) Screening Test, see *Phenylketonuria*

H

Health Manpower and Medical Associations (Ed.) ... 469

Hemolytic Anemia, see *Congenital Toxoplasmosis*

Hemolytic Disease of the Newborn—Review of Deaths in California, Earl Siegel, Robert F. Chinnock, Carol B. Hyman, Joseph H. Kushner, Talcott Bates, Arline Lewis, Arnold Gilbert and Leslie Corsa, Jr. (Or.) ... 81, 137

Hemorrhage, Gastrointestinal, Due to Rupture of an Aortic Homograft, Alex Gerber and Norman Rubaum (CR) ... 377

Hemorrhagic Shock, The Influence of Hyperbaric Oxygen Therapy on Metabolism, Yorke G. Jacobson, Melvin Keller, Eldred D. Mundth, Alfred J. DeFalco and James E. McClenethan (Or.) ... 93

Hepatitis, Post-transfusion, see *Control of*

Herniorrhaphy, Incisional and Inguinal, see *Marlex® Mesh*

Histoplasmosis—A Review of Three Cases Studied in San Diego County, V. J. Wyborney, Henry Walch, Alan B. Loeffler and Robert M. Wiita (Or.) ... 265

Human Growth Hormone, Effects of Treatment of, see *Achondroplastic Dwarfism*

Hyperbaric Oxygen in Therapy of Gas Gangrene—Report of a Case Following Induced Abortion, Karl L. Schaupp, Jr., Douglas Pinto and Rodney J. Valentine (Or.) ... 97

Hyperbaric Oxygen Therapy, see *Hemorrhagic Shock*

Hyperlipemia, Abdominal Pain and Growth Retardation (MSC) ... 297

Hyperpyrexia, see *Glutethimide Intoxication*

Hypertension, Recent Advances in the Treatment of, William M. Smith (Or.) ... 371

I

Impetigo—Bacteriologic Features and Renal Involvement, Stanton E. Shuler (Or.) ... 113

Incisional and Inguinal Herniorrhaphy, Marlex® Mesh in, James R. Johnson (Or.) 111

Income of Physicians, see *Sources of*

Inguinal and Incisional Herniorrhaphy, see *Marlex® Mesh*

Intraperitoneal Migration of a Kirschner Wire—Report of a Case, Eugene C. Weinstein, Takeshi Hayashida, P. L. Clark, III, and Alice L. Garrett (CR) 219

Intrauterine Contraceptive Device, see *Term Twin Pregnancy with*

K

Kirschner Wire, see *Intraperitoneal Migration*

L

Lactic Acidosis with Coma, Clinically Severe, John R. Payne (CR) 281

Larynx, Cancer of the, Results of Surgical and Radiological Treatment in One Institution, L. Henry Garland (Or.) 8

Latex Serologic Test for Syphilis—A New Screening Procedure, Charles M. Carpenter, Izabella O. Konya and Ronald A. LeClair (Or.) 167

Law and Sterilization, The, Peart, Baraty and Hassard (I) 323

Little League Shoulder—Osteochondrosis of the Proximal Humeral Epiphysis in Boy Baseball Pitchers, Joel E. Adams (Or.) 22

Long Acting Single Injection Caudal Anesthesia—1,208 Obstetrical Deliveries with Mepivacaine, Ronald E. Gunther and W. Benson Harer, Jr. (Or.) 424

Lung Cancer, Primary, Benjamin E. Kuchar (Or.) .. 182

M

Malignant Exophthalmos (MSC) 222

Management of Chronic Renal Failure (MSC) 45

Mandatory Tests for Phenylketonuria, Robert W. Day (Ed.) 50

Marlex® Mesh in Incisional and Inguinal Herniorraphy, James R. Johnson (Or.) 111

Measles Immunization Campaign—Public Health Report, Lester Breslow (CMA) 142

Medical Staff Conferences:
  Management of Chronic Renal Failure 45
  Reiter's Syndrome 129
  Malignant Exophthalmos 222
  Hyperlipemia, Abdominal Pain and Growth Retardation 297
  Vitamin D Resistant Rickets 383
  Cysticercosis 463

Medical Education, Continuing, for the Practicing Physician, Thomas B. Turner (CMA) 484

Medical Education, Continuing, Whither? Donald W. Petit (CMA) 485

Medical Student, The, Newlin Hastings (Or.) 35

Medicare and Medi-Cal to Date (Ed.) 305

Mepivacaine, see *Long Acting Single Injection*

Metabolism, Influence of Hyperbaric Oxygen Therapy on, see *Hemorrhagic Shock*

Methods of Therapy in Alcoholism, Max Hayman (Or.) 117

Methylphenidate, see *Glutethimide Intoxication*

Mineral Oil, see *Progressive Pulmonary Insufficiency*

Myeloproliferative Disorder and Tuberculosis, Irvin Herman (CR) 287

N

Neck Venous Hum in Adults, The, Arthur U. Rivin (Or.) 102

Necrotic Arachnidism, Martin I. Lewis and James F. Regan (Or.) 457

New Faculty Appointments (Ed.) 51

Newborn Deaths in California, see *Hemolytic Disease*

O

Obstetrics and Gynecology, Paracervical Block in, James E. Davis (Or.) 421

(Office Management of) The Chronically Draining Ear, James L. Sheehy (Or.) 31

Osteochondrosis of the Proximal Humeral Epiphysis in Boy Baseball Pitchers, see *Little League Shoulder*

Outside Look at Medical Education, An (Ed.) 391

Oxygen Therapy, Hyperbaric, see *Hemorrhagic Shock*

Oxyphenbutazone (Tandearil®) in Rhinoplasty, A Clinical Evaluation of Effectiveness, Byron J. Bailey and Alan M. Nahum (Or.) 271

P

Pain, Abdominal (MSC), see *Hyperlipemia*

Papillary Muscle, Rupture of, see *Differentiation of Dysfunction*

Paracervical Block in Obstetrics and Gynecology, James E. Davis (Or.) 421

Pericarditis, Pneumococcal in an Eight-Month-Old Child, Lawrence Madoff (CR) 208

Pesticide-Induced Illnesses, Pharmacology and Diagnosis, Rutherford T. Johnstone (Or.) 262

Pesticide-Induced Illness—Public Health Aspects of Diagnosis and Treatment, Irma West (Or.) 257

Pharmacology and Diagnosis of Pesticide-Induced Illnesses, Rutherford T. Johnstone (Or.) 262

Phenylketonuria: Early Detection, Diagnosis and Treatment, George C. Cunningham (Or.) 1
  Editorial, Robert W. Day 50

Phenylketonuria—The Guthrie Screening Test: A Method of Quantitation—Observation on Reliability and Suggestions for Improvement, Charles M. Blumenfeld, Mary Jean Wallace, and Ramona Anderson (Or.) 429

Physicians, Principal Employers of, see *Sources of Income*

PKU, see *Phenylketonuria*

Plague Warning, Lester Breslow (CMA) 64

Planing for Precancerous Skin—A Ten-Year Evaluation, Ervin Epstein (Or.) 26

Plastic Catheter Embolus, Radiographic Detection of, David R. Coblentz (Or.) 357

Pneumococcal Pericarditis in an Eight-Month-Old Child, Lawrence Madoff (CR) 208

Polyp, Benign Adenomatous, see *Primary Duodenal Carcinoma*

Post-transfusion Hepatitis, see *Control of*

Precancerous Skin, see *Planing*

Primary Duodenal Carcinoma Antedated by a Benign Adenomatous Polyp, Edwin S. Wilson, Jr. and James J. DuBois (CR) 379

Primary Lung Cancer, Benjamin E. Kuchar (Or.) 182

Problems of Aging—Public Health Report, Lester Breslow (CMA) 319

Progressive Pulmonary Insufficiency Due to Mineral Oil, Robert S. Eisenberg and William H. Oatway, Jr. (CR) 214

Proposed Constitutional Amendments for Action in 1967 (CMA) 401

Protein Losing Gastroenteropathy, Martin A. Pops (Or.) 201, 420

Psoriasis in Childhood, Eugene M. Farber and Ray A. Carlsen (Or.) 415
Psychosomatic Emergency, The, Charles William Wahl (Or.) 276
Public Health Aspects of Diagnosis and Treatment (of) Pesticide-Induced Illness, Irma West (Or.) 257
Pulmonary Air Embolism in Dogs, Experimental, Charles C. Wycoff and John E. Cann (Or.) 361
Pulmonary Artery Stenosis—A Frequent Part of the Congenital Rubella Syndrome, Joseph G. Ellis and William J. Kuzman (Or.) 435
Pulmonary Insufficiency, Progressive, Due to Mineral Oil, Robert S. Eisenberg and William H. Oatway, Jr. (CR) 214

Q

Quinidine Prophylaxis, see *Electrical Cardioversion*

R

Radiographic Detection of Plastic Catheter Embolus, David R. Coblentz (Or.) 357
Rational Basis for the Use of Spinal Anesthesia, A, Bruce M. Anderson (Or.) 307
Recent Advances in the Treatment of Hypertension, William M. Smith (Or.) 371
Records, Anesthetic and Recovery Room, John B. Dillon (Or.) 159
Recovery Room Records, see *Anesthetic*
Reiter's Syndrome (MSC) 129
Renal Failure, Chronic, Management of (MSC) 45
Renal Involvement and Bacteriologic Involvement (in) Impetigo, Stanton E. Shuler (Or.) 113
Retardation, Growth (MSC), see *Hyperlipemia*
Retroperitoneal Hematoma Following Retroperitoneal Pneumography, Paul S. Mahoney (CR) 381
Retroplacental Intrauterine Contraceptive Device, see *Term Twin Pregnancy*
Rheumatic Feevr—Summary of a Rheumatic Fever Workshop on Various Aspects of the Disease, Donald C. Fyler, Forrest H. Adams, Charles F. Pait and George C. Griffith (Or.) 11
Rickets, Vitamin D Resistant (MSC) 383
Rubella Nightmare, The, Harold K. Faber (Ed.) 228
Rubella Syndrome, Congenital, see *Pulmonary Artery Stenosis*
Rubella Syndrome—Cardiovascular Manifestations and Surgical Therapy in Infants, Donald R. Sperling and Joseph J. Verska (Or.) 340

S

Scalp, Angiosarcoma of the, see *Cystic Pulmonary Metastasis*
Skin, Precancerous, Planing for, A Ten-Year Evaluation, Ervin Epstein (Or.) 26
Skull Fracture, Congenital, James M. Dunn and Robert Raskind (CR) 125
Sources of Income and Principal Employers of California Physicians, August 1965—Report of the Bureau of Research and Planning (CMA). 70
(Spider Bite Poisoning), see *Necrotic Arachnidism*
Syphilis, see *Latex Serologic Test*

T

Tandearil® in Rhinoplasty, see *Oxyphenbutazone*
Television—The Newest Medium for Continuing Education in Medicine, Donald Brayton (CMA). 237
Term Twin Pregnancy with Retroplacental Intrauterine Contraceptive Device in Place, Albert F. Bartz (CR) 124
Therapeutic Abortion—Attitudes and Practices of California Physicians, Lawrence Sherwin and Edmund W. Overstreet (Or.) 337
Tokyo-Yokohama Asthma, A Review and Some Current Concepts, Rexford G. Haycraft (Or.) 89
Topical Cryotherapy—Use for Relief of Pain and Spasticity, Sedgwick Mead and Margaret Knott (Or.) 179
Toxoplasmosis, Congenital, with Hemolytic Anemia, Leslie G. Nelson and Joan E. Hodgman (CR) 454
Transfusions, Exchange, Advances in the Theory and Practice, Roderic H. Phibbs (Or.) 442
Traffic Accidents—Chronic Medical Conditions As a Cause, Julian A. Waller (Or.) 197
Treatment of Circulatory Disorders of the Lower Extremities, Harold M. Schneidman (Or.) 368
Tuberculosis and Myeloproliferative Disorder, Irvin Herman (CR) 287
Tuberculosis of Bone, Disseminated, Edwin S. Wilson, Jr. and Edward G. Whiting, Jr. (CR) 284
Twin Pregnancy, see *Term Twin Pregnancy*

V

Valve Replacement in Patients over Sixty, see *Cardiac*
Venereal Disease, Reporting of (CMA) 138
Venous Hum, Neck, in Adults, Arthur U. Rivin (Or.) 102
Viral Infections in Infants, see *Congenital Anomalies*
Vitamin D Resistant Rickets (MSC) 383

W

Whither Continuing Medical Education?, Donald W. Petit (CMA) 485
Wilbur Re-elected AMA Trustee (CMA) 138
WMA Declaration of Helsinki Serves as Guide to Physicians (I) 149

REVIEW ARTICLES

Protein Losing Gastroenteropathy, Martin A. Pops (Or.) 201, 420
Gout and Gouty Arthritis—Current Concepts and Management, Edward W. Boland (Or.) 249
Advances in the Theory and Practice of Exchange Transfusions, Roderic H. Phibbs (Or.) 442

EDITORIALS

Health Manpower and Medical Associations 469
Hemolytic Disease of the Newborn, Keith P. Russell 137
Mandatory Tests for Phenylketonuria, Robert W. Day 50
Medicare and Medi-Cal to Date 305
New Faculty Appointments 51
Outside Look at Medical Education, An 391
Rubella Nightmare, The 228

CALIFORNIA MEDICAL ASSOCIATION

Continuing Medical Education:
  Television—The Newest Medium for Continuing Education in Medicine, Donald Brayton 237
  Continuing Medical Education for the Practicing Physician, Thomas B. Turner 484
  Whither Continuing Medical Education?, Donald W. Petit 485

Council Meeting Minutes:
  521st Meeting, 7 May 1966 ... 52
  522nd Meeting, 18 June 1966 ... 229
  523rd Meeting, 30 July 1966 ... 309
  524th Meeting, 17 to 18 September 1966 ... 392
  525th Meeting, 29 October 1966 ... 471
Proposed Constitutional Amendments for Action in 1967 ... 401
Reporting of Venereal Disease ... 138
Wilbur Re-elected AMA Trustee ... 138

BUREAU OF RESEARCH AND PLANNING

Sources of Income and Principal Employers of California Physicians, August 1965 ... 70

INFORMATION

County/Teaching Hospitals—Statement of the CMA Council ... 74
Law and Sterilization, The, Peart, Baraty and Hassard ... 323
WMA Declaration of Helsinki Serves as Guide to Physicians ... 149

BOOK REVIEWS

Animal Behaviour and Drug Action—Ciba Foundation Symposium, *De Reuck and Knight* ... 155
Annual Review of Medicine, Vol. 16, 1965 and Vol. 17, 1966, *De Graff and Creger* ... 412
Arteriography—Principles and Techniques, *Curry and Howland* ... 327
Basic Gastro-Enterology, *Naish and Read* ... 243
Beck's Obstetrical Practice—8th Ed., *Taylor* ... 244
Blood Diseases of Infancy and Childhood, *Smith* ... 153
Carcinoma of the Alimentary Tract, *Burdette* ... 326
Cardiac Evaluation in Normal Infants, *Ziegler* ... 158
Cell, The, Its Organelles and Inclusions, *Fawcett* ... 330
Ciba Foundation Study Group No. 21—Hashish, *Wolstenholme and Knight* ... 247
Ciba Foundation Symposium—Animal Behavior and Drug Action, *De Reuck and Knight* ... 155
Ciba Foundation Symposium — Preimplantation Stages of Pregnancy, *Wolstenholme & O'Connor* .. 152
Clinical Obstetrics and Gynecology—Vol. 9, No. 1, Radiology in Obstetrics, *Siegler;* and Diseases of the Breast, *Escher* ... 245
Current Diagnosis, *Conn et al* ... 326
Current Psychiatric Therapies—Vol. VI—1966, *Masserman* ... 248
Diagnosis and Therapy of the Glaucomas—2nd Ed., *Becker and Shaffer* ... 156
Diagnostic Approach to Chest Diseases, *Lillington and Jamplis* ... 153
Diseases of the Breast, Escher, see *Clinical Obstetrics and Gynecology, Vol. 9, No. 1*
Disorders of Carbohydrate Metabolism in Infancy, *Cornblath and Schwartz* ... 243
Fine-Needle Aspiration Biopsy, Söderström ... 413
Fundamentals of Clinical Hematology—2nd Ed., Leavell and Thorup ... 156
Hallux Valgus, Allied Deformities of the Forefoot and Metatarsalgia, *Kelikian* ... 158
Handbook of Cardiology for Nurses—5th Ed., *Modell et al.* ... 411
Hashish—Ciba Foundation Study Group No. 21, *Wolstenholme and Knight* ... 247
Heritable Disorders of Connective Tissue—3rd Ed., *McKusick* ... 327
Hernia, *Nyhus and Harkins* ... 329
Immunopathology, *Grabar and Miescher* ... 328
Little Strokes, *Alvarez* ... 411
Lupus Erythematosus, *Dubois* ... 245
Management of Emotional Problems of Children and Adolescents, *Chapman* ... 248
Mayo Legacy, The, *Nagel* ... 152
Medical Care of the Adolescent—2nd Ed., *Gallagher* ... 411
Medical Department, U.S. Army in World War II—Medical Service in the Mediterranean and Minor Theaters, *Office of the Chief of Military History, Dept. of the Army* ... 328
Medical Department, United States Army, Surgery in World War II—Thoracic Surgery, Vol. II, *Office of The Surgeon General, Dept. of the Army* ... 156
Medical Service in the Mediterranean and Minor Theaters, see *Medical Department, U.S. Army in World War II* ... 328
Obstetrical Practice, Beck's—8th Ed., *Taylor* ... 244
Obstetrics, Williams—13th Ed., *Eastman and Hellman* ... 157
Ocular Pharmacology, *Havener* ... 414
Operable Heart Disease, *Sirak* ... 326
Operative Obstetrics—2d Ed., *Douglas and Stromme* 156
Oral Antidiabetic Therapy 1956-1965: With Particular Reference to Tolbutamide (Orinase), *Tucker*.. 158
Outline of Radiographic Findings in Multiple-System Disease, An, *Simonton and Jamison* ... 155
Pathology, Vols. I and II—5th Ed., *Anderson* ... 325
Pathology Annual: 1966, Vol. 1, *Sommers* ... 327
Pediatric Electrocardiography, *Guntheroth* ... 244
Pediatric Therapy—2nd Ed., *Shirkey* ... 243
Pediatrician's Ophthalmology, The, *Liebman and Gellis* ... 413
Pharmacology and Patient Care—2nd Ed., *Garb and Crim* ... 247
Pharmacology and Therapeutics—6th Ed., *Grollman* ... 247
Preimplantation Stages of Pregnancy—Ciba Foundation Symposium, *Wolstenholme and O'Connor* 152
Preventive Medicine for the Doctor in His Community—3rd Ed., *Leavell and Clark* ... 246
Principles of Pathology—2nd Ed., *Hopps* ... 244
Progress in Clinical Cancer—Vol. II, *Ariel* ... 412
Psychopathology of Perception, *Hoch and Zubin* 154
Psychopathology of Schizophrenia, *Hoch and Zubin* 325
Radiographic Atlas of the Genitourinary System, *Ney and Friedenberg* ... 412
Radiographic Examination in Blunt Abdominal Trauma, *McCort* ... 329
Radiologic Diagnosis in Infants and Children, *Brodeur* ... 247
Radiology in Obstetrics, *Siegler*, see *Clinical Obstetrics and Gynecology, Vol. 9, No. 1*
Roentgen Signs in Clinical Practice—Vols. I and II, *Meschan* ... 412
Shock and Hypotension, *Mills and Moyer* ... 246
Shoulder Pain, *Cailliet* ... 330
Spontaneous Regression of Cancer, *Everson and Cole* ... 412
Surgery—3rd Ed., *Moyer et al* ... 245
Surgery in World War II—Thoracic Surgery, Vol. II, see *Medical Department, U.S. Army* ... 156
Surgical Approaches to the Neck, Cervical Spine and Upper Extremity, *Kaplan* ... 414
Symposium on Surgery of the Ocular Adnexa, *New Orleans Academy of Ophthalmology* ... 413
Symposium on Vascular Disorders of the Eye, *Bettman* ... 153
Synopsis of Obstetrics—7th Ed., *McLennan* ... 244
Thoracic Surgery—Vol. II, see *Medical Department, U.S. Army*
To-Day's Drugs, *British Medical Journal* ... 411
Today's Health Guide (W. W. Bauer, Editor), American Medical Association ... 329
Viruses Inducing Cancer, *Burdette* ... 328
Vitreoretinal Pathology and Surgery in Retinal Detachment, *Cibis* ... 248
Williams Obstetrics—13th Ed., *Eastman and Hellman* ... 157
Your Ulcer: Prevention, Control, Cure, *Serino* ... 153

DEATHS

Albert, Walter, Los Angeles, 29 Aug. 1966 ... 315
Albronda, Henry F., San Francisco, 30 Oct. 1966 ... 481
Allen, Albert, San Pedro, 17 June 1966 ... 403
Argens, Richard, Imola, 23 June 1966 ... 139
Ashcraft, Granville P., Yreka, 19 July 1966 ... 236
Badertscher, Victor A., Dinuba, 4 July 1966 ... 139
Ball, Howard A., San Diego, 24 Aug. 1966 ... 315
Baxter, Frank Stanley, Oakland, 22 Aug. 1966 ... 315
Becker, Harry Fred, Van Nuys, 12 June 1966 ... 139
Belisle, Rex C., Escondido, 11 Sept. 1966 ... 403
Benson, Kenelm Winslow, Berkeley, 3 Oct. 1966 ... 403
Bramkamp, Robert G., San Bernardino, 14 Sept. 1966 ... 481
Brown, F. Earl, Los Angeles, 28 June 1966 ... 139
Burch, Bernard Owen, Livermore, 17 May 1966 ... 62
Calvy, Lloyd Edward, Orange, 13 Oct. 1966 ... 481
Carlson, Albert Steen, Ontario, 7 June 1966 ... 139
Carroll, William A., San Francisco, 16 Sept. 1966 ... 403
Chamberlain, Robert W., Tehachapi, 11 May 1966 ... 62
Chambers, Eleanor Kathleen, Berkeley, 4 July 1966 ... 236
Cherry, Walter Smith, Rialto, 22 Sept. 1966 ... 403
Chiapella, Joseph Octave, Chico, 20 April 1966 ... 315
Chole, Arthur Steven, Encino, 23 Aug. 1966 ... 315
Clayton, James O., Redondo Beach, 21 June 1966 ... 481
Davis, Harold LeRoy, Sunnyvale, 23 Oct. 1966 ... 481
Dayton, Glenn Orville, Sr., Los Angeles, 23 Oct. 1966 ... 481
Doren, Neil C., Los Angeles, 22 Sept. 1966 ... 403
Dykes. H. Robert, Sr., Santa Monica and Taft, 23 Aug. 1966 ... 315
Eberhardt, Gustav, Gonzales, 22 June 1966 ... 315
Edmond, Julian, Modesto, 19 June 1966 ... 139
Eymundson, Kristbjorn S., San Francisco, 22 May 1966 ... 62
Fischer, Siegfried, San Francisco, 30 June 1966 ... 139
Fletcher, Charles D., San Francisco, 13 May 1966 ... 62
Fluhmann, C. Frederic, San Francisco, 12 June 1966 139
Francis, Raymond T., Santa Ana, 8 Sept. 1966 ... 403
Fricke, Albert A., Los Angeles, 7 Oct. 1966 ... 481
Gallas, Digby, Los Angeles, 10 Oct. 1966 ... 481
Galt, Curtis Martin, Manteca, 10 March 1966 ... 62
Garfield, F. Edwyn, San Francisco, 25 July 1966 ... 236
Garland, L. Henry, San Francisco, 31 Oct. 1966..480, 481
Gehres, Robert F., Sacramento, 30 July 1966 ... 236
Gittleman, Ben, Los Angeles, 23 Oct. 1966 ... 481
Glogauer, Otto L., Long Beach, 26 Sept. 1966 ... 403
Hawkins, William J., Arcadia, 7 June 1966 ... 139
Henley, R. Bruce, Oakland, 27 Aug. 1966 ... 403
Henry, Boyd D., Los Angeles, 27 Sept. 1966 ... 481
Herzog, Paul, Tarzana, 29 June 1966 ... 139
Hinman, Harry Thornton, Jr., Shasta, 27 July 1966 ... 236
Hurwitz, Samuel Haymann, San Francisco, 31 Aug. 1966 ... 315
Illick, Charles Raymond, Santa Paula, 24 Sept. 1966 ... 481
Ingham, Samuel D., Los Angeles, 17 Feb. 1966 ... 62
Isnardi, Mario, San Francisco, 28 July 1966 ... 236
Jablonski, John J., San Bernardino, 9 April 1966 ... 139
Jones, Dwight Harold, Bakersfield, 7 Aug. 1966 ... 315
Kaplan, Max, Los Angeles, 25 July 1966 ... 236
Kasper, Raymond J., Fresno, 11 July 1966 ... 403
Keller, Samuel H., Riverside, 17 Sept. 1966 ... 403
Kibler, Robert Scott, San Bernardino, 6 July 1966 ... 315
King, Gordon G., San Francisco, 25 Aug. 1966 ... 403
Krutchkoff, Morris, San Rafael, 24 May 1966 ... 62
Kuhlmann, Frederic William, Long Beach, 17 Jan. 1966 ... 62
Lacoe, Jeremiah Ralph, Los Angeles, 22 Oct. 1966 ... 481
Lawyer, Paul Carey, Inglewood, 4 June 1966 ... 62
Layman, John D., Pasadena, 19 June 1966 ... 139
Lee, Charles F., Jr., Palo Alto, 30 July 1966 ... 315
Lenert, Charles, Sacramento, 26 Oct. 1966 ... 481
Lindenberg, Fred, Los Angeles, 22 Sept. 1966 ... 403
Lindsay, William W., San Francisco, 21 June 1966 ... 482
Lopizich, Ivo John, Los Angeles, 22 July 1966 ... 236
Lugosy, Laszlo, Los Angeles, 7 June 1966 ... 62
Lutz, Gustav A., Glendale, 23 June 1966 ... 139
Markolf, Harry Foster, Pasadena, 28 Aug. 1966 ... 315
McClurkin, Arthur Archibald, Los Angeles, 17 July 1966 ... 236
McLaughlin, Tilman Henry, Los Angeles, 23 July 1966 ... 236
Mendelsohn, Howard Abraham, Beverly Hills, 15 Sept. 1966 ... 403
Merrill, Harry Palmer, Los Angeles, 30 June 1966 ... 139
Miles, Seth Herbert, Los Angeles, 29 May 1966 ... 62
Myers, R. (Rudolf) B. S., Santa Monica, 6 Sept. 1966 ... 404
Newman, Alfred, San Francisco, 20 May 1966 ... 62
Norcross, Howard B., Los Angeles, 25 Sept. 1966 ... 404
O'Connor, Vincent D., Carmel Valley, 4 Sept. 1966 ... 316
Oddo, Nicholas Vincent, Long Beach, 10 June 1966 139
O'Neil, Francis H., Eureka, 25 July 1966 ... 316
Osborne, Roland Harris, Santa Monica, 29 Oct. 1966 ... 482
Petch, Philip Henry, Oakland, 20 Oct. 1966 ... 482
Poley, Cyrus Watt, El Sereno, 9 Aug. 1966 ... 316
Powell, Lyle S., San Diego, 1 June 1966 ... 62
Ransom, Jack Kennedy, Modesto, 26 June 1966 ... 482
Rees, Charles W., San Diego, 9 Oct. 1966 ... 482
Robarts, Harry P., San Francisco, 23 July 1966 ... 236
Roberts, Gordon W., Oakland, 2 Sept. 1966 ... 316
Robertson, Donald Logan, Modesto, 27 Oct. 1966 ... 482
Rosenfeld, Maurice H., Los Angeles, 24 Oct. 1966 ... 482
Rubenstein, Harry, Canoga Park, 24 July 1966 ... 236
Sale, J. Judson, San Francisco, 3 Sept. 1966 ... 404
Sand, Charles A., San Diego, 28 Aug. 1966 ... 316
Schillinger, Robert J., Los Angeles, 2 Sept. 1966 ... 404
Shah, Aurang, Sacramento, 26 Aug. 1966 ... 316
Sharpsteen, Jay Randolph, Oakland, 16 Aug. 1966 ... 316
Shepardson, Dwight Emerson, Redwood City, 13 Feb. 1966 ... 139
Smith, Gibson Carr, San Diego, 22 Sept. 1966 ... 482
Smith, W. Burr, Los Angeles, 4 June 1966 ... 236
Steen, Claude Earl, Fullerton, 23 Aug. 1966 ... 482
Suraci, Rocco T., Oakland, 2 Nov. 1966 ... 482
Svoboda, Frank Charles, San Diego, 7 Oct. 1966 ... 482
Trainor, Romaine R., San Diego, 5 July 1966 ... 139
Trott, Leslie DeNyse, Glendale, 14 Sept. 1966 ... 404
Van Cott, Wesley Bailey, Los Angeles, 20 Oct. 1966 ... 482
Whitcomb, Edith Lucy, Los Angeles, 30 May 1966 ... 62
Whittaker, Lawrence F., Huntington Beach, 24 July 1966 ... 236
Wilkinson, Henry Fielding, San Gabriel, 12 Aug. 1966 ... 482
Williams, Edward K., San Mateo, 8 Sept. 1966 ... 404

"The response in most cases is dramatic..."

Lowell, J. B.: New England J. Med. 269: 798, 1963.

When Lowell added phenylbutazone to his usual immobilization and rest measures for the treatment of acute shoulder bursitis, he found "The response is dramatic and occurs within forty-eight to seventy-two hours, and occasionally as early as twenty-four hours. There is rapid loss of pain and concomitant increase in available motion".

quently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possible side effects.

Confusional states, hyperglycemia, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Average Dosage: Initially, give 400 mg. daily (one tablet or capsule q.i.d.), reducing this, if possible, when a favorable therapeutic effect has been obtained. If after one week there has been no response, discontinue the drug.

For complete details, please refer to full prescribing information. 6509-V(B)

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

BU-4513

Butazolidin® alka Geigy

Each capsule contains: Butazolidin®, phenylbutazone, 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate, 150 mg.; homatropine methylbromide, 1.25 mg.

The discomforts of

DIARRHEA
MUCOUS COLITIS
DIVERTICULITIS
SPASTIC URETERITIS
BLADDER SPASM

are relieved by
direct musculotropic action
with.....

Trocinate®
BRAND THIPHENAMIL HCl

Available in 100 milligram pink sugar-coated tablets.

The high therapeutic index permits dosage sufficient to relieve spasm promptly.

Administer 4 tablets every 4 hours until relief is constant, then adjust maintenance dosage.

Trocinate *BRAND* THIPHENAMIL HCl

Directly relaxes smooth muscle spasm
Combats hypermotility
Non-mydriatic, may be used in glaucoma

Sixteen years of clinical use, with absence of untoward effects, has established the safety and effectiveness of Trocinate.

Trocinate is metabolized in the body and completely eliminated, which is a safety factor. Dosage must be sufficient to maintain the therapeutic blood level.

DISPENSED IN BOTTLES OF
100, 250 AND 2000 TABLETS

Literature and samples sent upon request

WM. P. POYTHRESS & CO., INC.
RICHMOND, VIRGINIA
Manufacturers of ethical pharmaceuticals since 1856

Dieting Results in an Anti-Coronary Club

(Continued from Page 33)

office in an effort to reverse the risk factors affecting his patients," the article said.

If these results are confirmed by other studies in progress, "there is reason to hope that progress can be made in deterring the nation's paramount public health problem," the report said.

The authors are George Christakis, M.D., Seymour H. Rinzler, M.D., Morton Archer, M.B.A., M.P.H., and Arthur Kraus, Sc.D., all of the New York City Department of Health.

Publications on Respiratory Diseases Are Ready for Distribution

Two new publications on emphysema and chronic bronchitis, "Chronic Respiratory Diseases, a Growing Menace" and "Management of Chronic Obstructive Respiratory Diseases," were released recently by the Public Health Service, U.S. Department of Health, Education, and Welfare.

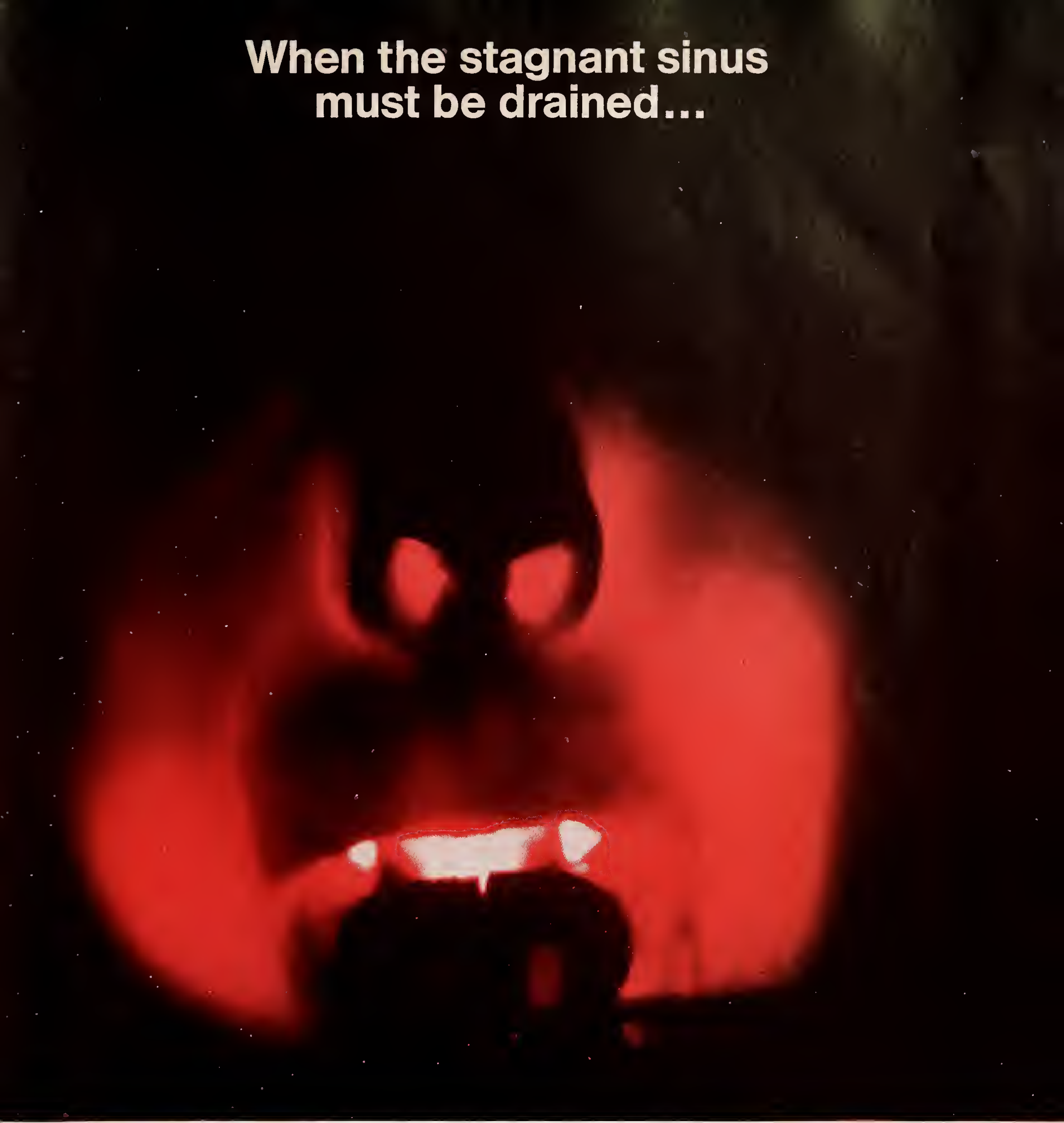
Emphysema and chronic bronchitis are becoming one of the Nation's most urgent health problems, as evidenced by the growing numbers of people killed and crippled by these pulmonary disorders. The number of deaths caused by these diseases had quadrupled during the last decade for which records are available, and there is no indication of any decrease in the trend. Emphysema is a crippling disease, and according to Social Security disability statistics, causes more invalidism than such well-known cripplers as cancer, stroke, tuberculosis or mental disorders.

The publications are initial efforts of the Public Health Service's recently-created Chronic Respiratory Diseases Program, which is charged with providing the medical community and the general public with the latest information on control of these diseases and with demonstrating that detection, treatment and rehabilitation can help stem the potential epidemic of chronic respiratory diseases.

"Chronic Respiratory Disease, A Growing Menace," PHS Publication No. 1445, describes the increasing significance of these diseases and outlines the functions and activities of the new PHS control program.

"Management of Chronic Obstructive Respiratory Diseases," PHS Publication No. 1457, is a resume of the Eighth Annual Emphysema Conference held in Aspen, Colorado, in June 1965. The booklet was edited by Thomas L. Petty, M.D., of the University of Colorado Medical Center. The conference, sponsored by the Public Health Service brought together leading authorities in emphysema to discuss up-to-date methods for treatment and care of respiratory victims. The Aspen publication contains sections on definitions, respiratory

(Continued on Page 63)



Transillumination of the sinuses—diffuse shadow on right side of face indicates unilateral maxillary sinusitis.

In the common cold, Neo-Synephrine is unsurpassed for reducing nasal turgescence. It stops the stuffy feeling at once. It opens sinus ostia to re-establish drainage and lessen the chance of sinusitis. With Neo-Synephrine, in the concentrations most commonly used, decongestion lasts long enough for extended breathing comfort, without endangering delicate respiratory tissue. Systemic side effects are virtually unknown. There is little rebound tendency.

Winthrop Laboratories, New York, N.Y. 10016 Winthrop

Neo-Synephrine® HCl

Brand of phenylephrine hydrochloride

is available in a variety of forms, for all ages:

- ⅛% solution for infants
- ¼% solution for children and adults
- ¼% pediatric nasal spray for children
- ½% solution for adults
- ½% nasal spray for adults
- ½% jelly for children and adults
- 1% solution for adults (resistant cases)

Also NTZ® Solution or Spray
Antihistamine-decongestant

Use of Seat Belts Is Urged For Decrease in Traffic Fatalities

"More people have seat belts in their cars than ever before. Many riders, however, especially occupants of the newer models, risk death by failing to wear them."

Researchers at Cornell Aeronautical Laboratory, Inc. of Buffalo, New York, report this finding from a study of a selected group of automobile accidents from 1956 to 1965. The study was supported by the Public Health Service's Division of Accident Prevention and the Automobile Manufacturers Association.

New cars, beginning in 1964, have had seat belts as standard equipment in the front seat. Beginning with the 1966 models, seat belts have been standard equipment in front and back seats.

The report found that only 30 per cent of the people in 1965 model automobiles were wearing their seat belts in the accidents under study. Thirty-seven per cent of the occupants of 1961-62 models were wearing their belts.

"It has been estimated that the lives of 5,000 persons would be saved every year if everyone wore seat belts," said Dr. Paul Joliet, Chief of the Division of Accident Prevention.

"Drivers and their passengers owe it to themselves and to their families to wear seat belts now being provided for them. The deaths of persons in automobile accidents are even more tragic when the seat belts that might have saved them are found lying unused," Dr. Joliet said.

Swiss Doctor Receives 1965 Gould Award

The William and Harriet Gould Foundation announces the recipient of the 1965 Gould Award: Professor Dr. Richard Luchsinger of Zurich, Switzerland. Dr. Luchsinger was honored for his outstanding contributions to the science of Phoniatry. The award was presented to the recipient in person at the recent annual meeting of the Society for Speech and Voice Science in Saarbrücken, Germany.

The Gould Award is presented annually for outstanding fundamental contributions in the field of laryngology. The recipient is selected by an international committee which at present consists of P. Dr. Julius Berendes, Universitäts Hals-Nasen-Ohren-Klinik, Marburg (Lahn), Germany; P. Dr. Carl-Axel Hamberger, Karolinska Sjukhuset, Stockholm 60 Sweden; Dr. Jo Ono, 75 Zaimokucho Azabu, Minato-ku, Tokyo, Japan; and Dr. Hans von Leden, Institute of Laryngology and Voice Disorders, Los Angeles, California 90025, Chairman.

The Award consists of an illuminated plaque and a cash prize. Nominations for the 1966 award should be filed with one of the committee members as soon as possible.

THINK Towne when you think

GENERICS

In medicine and in pharmacy only the BEST is good enough. When you prescribe generically specify the manufacturer's name.

Play it safe ... Specify Towne

So your patient will consistently receive the highest quality and uniformity.

Product List available on request.

One of hundreds of TOWNE QUALITY GENERICS.

Towne PRESCRIPTION PRODUCTS DIVISION

Towne, Paulsen & Company, Inc.
Pharmaceutical Chemists Monrovia, California

autions and adverse reactions: The transitory drowsiness which
occur with hydroxyzine HCl usually disappears spontaneously
ew days with continued therapy, or is correctable by dosage
ction. Dryness of the mouth may be seen with higher doses.
untary motor activity, including rare instances of tremor and
ulsions, has been reported, usually on higher than recom-
ed dosage. **Hydroxyzine HCl may potentiate barbiturates,**
otics such as meperidine, and other CNS depressants. In con-
ve use, dosage for these drugs should be decreased as much
%. Because drowsiness may occur, patients should be cau-
d against driving a car or operating dangerous machinery.
nteral Solution Precautions and contraindications: This dos-
form is intended only for I.M. or I.V. administration and
d not, under any circumstances, be injected subcutaneously
tra-arterially. When the usual precautions for I.M. injection
been followed, reports of soft tissue reactions have been
When used intravenously, if given undiluted, minimal amounts
emolysis (2-3 grams of liberated hemoglobin) will occur. If
ed with 50 cc. of normal saline and given during a period of
minutes or more, this phenomenon does not occur. Due to the
e, and infrequent phlebitis, the rate of injection must not
ed 25 mg. per minute. A single I.V. administration in excess of
g. is not recommended. Particular care should be used to
e injection only into intact veins; a few instances of digital
rene occurring distal to the injection site have been attributed
advertent intra-arterial injection or periarterial extravasa-
both of which should be avoided. **Use in Pregnancy:** When
nistered to rats at high dosage, hydroxyzine induced fetal
rmalities. Until human clinical data are available adequate
ablish safety in early pregnancy, hydroxyzine is contraindi-
in early pregnancy.

Publications on Respiratory Diseases Are Ready for Distribution

(Continued from Page 44)

failure, right heart failure and pulmonary hypertension, antibiotics and infections, home and clinic care, pharmacologic agents, and surgery.

Although many physicians are uncomfortable about providing treatment for a disease about which so little is known, participants of the conference overwhelmingly agreed that medical practitioners should be encouraged to provide proper treatment and care to the respiratory patients they are seeing in ever-increasing numbers.

Both "Chronic Respiratory Diseases, A Growing Menace" and "Management of Chronic Obstructive Respiratory Diseases" are being mailed to physicians throughout the country. In addition, single copies are available from the Public Health Service, Department of Health, Education, and Welfare, Washington, D.C. 20201. The booklets may be purchased in quantity from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402, at 30 cents a copy, or $22.50 per 100 copies.

Hawaii Is 1967 Site for Forensic Sciences Meeting

The annual meeting of the American Academy of Forensic Sciences will be held February 20 to 25, 1967, at the Princess Kaiulani Hotel in Honolulu.

The American Academy of Forensic Sciences was founded in 1948 to centralize the various disciplines of the forensic sciences in order to promote the use of scientific methods and knowledge in the solutions of legal problems and controversies; to improve professional qualifications of scientists engaged in the assistance of the courts and attorneys; and to develop and extend a better understanding of the application of legal doctrines to scientific professions.

The Academy encompasses the disciplines of toxicology, pathology, psychiatry, questioned documents, criminalistics and forensic jurisprudence. The current membership consists of more than 700 acknowledged leaders in these forensic fields.

The President of the Academy is Jack L. Sachs, LL.B., 1 North La Salle Street, Suite 855, Chicago, Illinois 60602; and the Secretary-Treasurer is Samuel R. Gerber, M.D., LL.B., 2121 Adelbert Road, Cleveland, Ohio 44106.

As host for the meeting, Alvin V. Majoska, M.D., has issued an invitation to all those interested in such disciplines. For further information and for a copy of the scientific program, write to Doctor Majoska, Office of the Medical Examiner, City and County of Honolulu, 1455 South Beretania Street, Honolulu, Hawaii 96814.

only one in the morning
and one in the evening